CLINICAL PRACTICE GUIDELINES

AUTISM SPECTRUM DISORDER

IN CHILDREN AND ADOLESCENTS

2ND EDITION (2023)

ACADEMY OF MEDICINE SINGAPORE

COLLEGE OF PAEDIATRICS AND CHILD HEALTH, SINGAPORE

COLLEGE OF PAEDIATRICS AND CHILD HEALTH, SINGAPORE (CPCHS)

CLINICAL PRACTICE GUIDELINES ON AUTISM SPECTRUM DISORDER IN CHILDREN AND ADOLESCENTS

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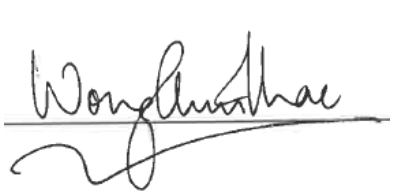

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CPG WORKGROUP CO-LEADS
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- **R** = Key Recommendation
- **GPP** = Good Practice Point

CHAPTER 1: SCREENING AND DIAGNOSIS

GPP 1.1 Professionals should identify autism early, because early identification provides the opportunity for prompt referral and intervention, which may lead to improved long-term outcomes. [EM1-1]

GPP 1.2 Surveillance for early signs of autism should be embedded in a national developmental surveillance programme. [EM1-1]

GPP 1.3 Developmental surveillance should be performed on several occasions at periodic intervals so that the signs of autism can be detected. [EM1-2]

GPP 1.4 Caregivers' concerns about a child's communication, social interaction, play and behaviour should be elicited at every well-child clinic visit. Caregivers' attention should be drawn to the 'Parental Concerns' items in the Child Health Booklet, and they should be encouraged to inform healthcare professionals if their child shows any of these difficulties. [EM1-3]

GPP 1.5 Preschool teachers' concerns about a child's communication, social interaction, play and behaviour should be elicited in preschool developmental surveillance programmes. [EM1-3]

GPP 1.6 Professionals should initiate early specialist referrals for preschool children with concerns related to communication, social interaction, play or behaviour, instead of reassuring parents or adopting a wait-and-see attitude. [EM1-4]

GPP 1.7 Children with one or more of the following clinical features should be referred promptly for comprehensive developmental evaluation [EM1-5]:

- Any regression or loss of language or social skills
- No babbling, use of gestures (waving bye, pointing), shared enjoyment (spontaneous showing, following point/gaze), or response to name by 12 months
- No single words, following of instructions, or pretend play by 18 months
- Lack of eye contact or social response, or any unusual repetitive, rigid, obsessive, or sensory behaviours at any age

GPP 1.8 Professionals should remain vigilant for possible autism in any child or adolescent with ongoing difficulties relating to communication, social interaction, behaviour or mental health. [EM1-5]

GPP 1.9 Healthcare professionals should be aware of the factors associated with an increased likelihood for developing autism, and may consider targeted screening for children presenting with developmental concerns or these factors. Specific factors associated with increased likelihood of autism include:

- History of autism in a sibling
- Prematurity of <35 weeks' gestation or birth weight <2500g
- History of neonatal hypoxic encephalopathy
- Having a genetic syndrome known to be associated with autism
- Intrauterine exposure to maternal anti-epileptic medication

- Advanced parental age at child's birth (>40 years of age)
- Parental history of mental health condition.

[EM1-6, 1-9 and 2-2. Please see Chapter 2 (Sections 2.1 and 2.2) for additional information]

R 1.10 Based on current evidence, the universal use of autism-specific screening tools in the general paediatric population with no risk factors is not recommended. [EM1-7]

R 1.11 Where there are concerns for developmental delay in children, the application of an autism-specific screening tool can supplement the clinical judgement of healthcare professionals, but should not be used as the sole reason to initiate specialist referral or to exclude a diagnosis of autism. [EM1-7]

GPP 1.12 Professionals who decide to implement the use of an autism screening tool should be aware of the performance characteristics (e.g., false positives, false negatives) and limitations of the tool, and that performance characteristics can vary across different cultures and contexts. [EM1-7]

R 1.13 Autism-specific screening tools should be used within the age range for which they are validated. Professionals should be aware that the accuracy of screening tools has been found to be better for older toddlers (i.e., estimated 21 months old and older), than for younger toddlers (i.e., 12 months old to 20 months old). [EM1-8]

GPP 1.14 Although research has found group differences in neurophysiological and other biomarkers between children on the autism spectrum and those without, these are not yet sufficiently developed to be accurate or reliable screening tools for autism. Based on current evidence, isolated neurophysiological and other biomarkers are not recommended for routine clinical use in screening for autism. [EM1-10]

GPP 1.15 Professionals involved in diagnosing autism in children and adolescents should use the current version of either the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD), and should state which classification system was used. [EM1-11]

GPP 1.16 Professionals involved in the diagnostic assessment of autism spectrum disorder (ASD) should be aware that some children may not meet diagnostic criteria on the DSM-5-TR when they would have done so on the DSM-IV-TR. Some of these children may meet a diagnosis of Social Communication Disorder instead, and may still need interventions similar to those on the autism spectrum. [EM1-11]

GPP 1.17 Children being evaluated for autism should have (or be referred for) a medical examination, in order to facilitate a comprehensive evaluation and further medical treatment if needed. [EM1-12]

GPP 1.18 A multi-disciplinary approach is recommended for the diagnosis of ASD in children and adolescents as far as practically possible, particularly in complex cases or cases where the single clinician determines that high diagnostic confidence cannot be achieved alone. [EM1-13]

GPP 1.19 A single-clinician approach to the diagnosis of ASD may be considered when the following conditions are met: [EM1-15]

- Conducted by specialist medical practitioners or psychologists with adequate training and experience in diagnosing autism in children and adolescents (see Table 1.6).
- Include multi-source feedback from various settings in order to obtain a comprehensive picture of the child being assessed [EM1-16].
- Include direct observation and interaction with the child being assessed.

- Include thorough contemporaneous documentation on the child's symptoms of autism that meet the prevailing international diagnostic criteria for ASD (e.g., DSM-5-TR) [EM1-11].

R 1.20 Assessment and diagnosis of ASD should not solely rely on autism-specific diagnostic instruments, but should encompass a holistic profile of the child including developmental, medical, and social history, physical examination, consideration of differential diagnoses and co-existing conditions, cognitive, sensory, academic and adaptive behaviour profiles, as well as strengths, skills and needs to facilitate management plans. Autism-specific diagnostic instruments can complement the assessment process and supplement clinical observation and information collection. [EM1-14]

GPP 1.21 Information gathered to make a diagnosis should include reports on or observations of the child in the home, community or outside the clinic setting. [EM1-16]

GPP 1.22 Professionals involved in the diagnostic process should consider that females on the autism spectrum may present with a different symptom profile and level of needs as compared to males with autism. [EM1-17]

GPP 1.23 Professionals should be aware of cultural differences when assessing for autism. Understanding these cultural variations in appropriateness of behaviour would help the professional to cater their assessment to patients from different cultural backgrounds. [EM1-18]

GPP 1.24 Professionals should be aware that there are overlapping features between intellectual disability (ID) and autism when assessing for autism in individuals with an intellectual disability. Autism should not be diagnosed if symptoms are better accounted for by ID. [EM1-19

CHAPTER 2: AETIOLOGY AND INVESTIGATIONS

GPP 2.1 Healthcare professionals should be aware of the strong genetic heritability of autism and monitor for features of autism in children who have siblings and/or first-degree relatives on the autism spectrum. [EM2-1]

GPP 2.2 Healthcare professionals should be aware that some genetic conditions or syndromes may be associated with autism and should monitor the affected child for features of autism. Examples of genetic conditions or syndromes include Fragile X syndrome, Angelman syndrome, Tuberous Sclerosis, Rett syndrome, PTEN Hamartoma syndrome and Down Syndrome. [EM2-1]

GPP 2.3 Healthcare professionals should be aware that there is insufficient evidence for any association between maternal ingestion of paracetamol during pregnancy and the probability of autism in their offspring. Pregnant mothers do not need to avoid paracetamol ingestion in pregnancy if it is indicated. [EM2-3]

GPP 2.4 Healthcare professionals should discuss the indications and side-effects of various anti-epileptic medications with pregnant women requiring such treatment, because there is evidence linking certain types of maternal anti-epileptic medication (especially sodium valproate) in pregnancy with the probability of developing autism in their offspring. [EM2-4]

GPP 2.5 Healthcare professionals should be aware that there is insufficient evidence for any association between the use of epidural analgesia for labour/delivery in women and the probability of autism in their offspring. Pregnant mothers in labour do not need to avoid epidural analgesia if deemed necessary. [EM2-5]

GPP 2.6 Parents should be reassured that childhood vaccinations are not associated with autism, and should proceed with their child's vaccination schedule as recommended on the National Immunization Schedule. Healthcare professionals should continue to provide nationally recommended childhood vaccinations to children on the autism spectrum, including the Measles, Mumps, Rubella (MMR) vaccine. [EM2-6]

GPP 2.7 Routine heavy metal (i.e., antimony, aluminium, arsenic, cadmium, lead, manganese, mercury, nickel, silver, and thallium) concentration testing or screening is not recommended for children on the autism spectrum as there is insufficient evidence for any causative link. [EM2-7]

GPP 2.8 Healthcare professionals may consider investigating for mercury toxicity in selected children on the autism spectrum who present with serious neurological and immunological problems. [EM2-7]

GPP 2.9 Healthcare professionals may consider investigating for lead toxicity in selected children on the autism spectrum where pica is suspected or diagnosed. [EM2-7]

GPP 2.10 Children who present with autism and have additional clinical features suggestive of an underlying genetic condition (such as microcephaly, seizures, dysmorphic features, congenital anomalies or a positive family history of developmental disability) should be referred to a genetic specialist for diagnostic confirmation and counselling. Examples of genetic conditions or syndromes include Fragile X syndrome, Angelman syndrome, Tuberous Sclerosis, Rett syndrome, PTEN Hamartoma syndrome and Down Syndrome. [EM2-1]

GPP 2.11 Children who are diagnosed with autism may benefit from genetic testing which can be offered by healthcare professionals. Discussion on the exact genetic test(s) to consider should be conducted by a genetic specialist or similarly-trained professional. [EM2-1]

GPP 2.12 Magnetic resonance imaging (MRI) of the brain may be performed in selected children on the autism spectrum who present with microcephaly, milestone regression or where structural brain lesions are suspected. [EM2-8]

GPP 2.13 Electroencephalography (EEG) may be performed in selected children on the autism spectrum who develop clinical seizures, seizure-like movements and/or regression of developmental milestones. [EM2-8]

GPP 2.14 Targeted screening for an inborn error of metabolism (IEM) may be indicated in selected children on the autism spectrum who present with clinical features such as cyclic vomiting, microcephaly, ataxia, epilepsy, intellectual disability or have a family history of consanguinity. [EM2-8]

GPP 2.15 Routine stool investigations to test for yeast or microbiota profile are not recommended for children on the autism spectrum. [EM2-8]

CHAPTER 3: INTERVENTION

R 3.1 Augmentative and Alternative Communication (AAC) may be used for children and adolescents on the autism spectrum to support communicative understanding and expression. The AAC system should be customized to the individual's communication needs, preferences and environment. [EM3-1]

R 3.2 Cognitive Behavioural Therapy (CBT) may be used for children and adolescents on the autism spectrum who have sufficient verbal and reasoning abilities, to address emotion-related issues such as anxiety and anger. Modifications may be required to facilitate

understanding and application of CBT strategies in this population. Involvement of caregivers can support the generalization of strategies for younger children. [EM3-2]

R 3.3 Communication-based interventions (e.g., language training, pivotal response training) may be used for children and adolescents on the autism spectrum as they lead to improved social communication outcomes (including joint attention, social engagement and initiation), and may lead to improved receptive language, expressive language, and speech prosody outcomes. [EM3-3]

R 3.4 Developmental interventions, (a group of interventions that are implemented based on developmental sequence and focus on supporting children's learning of skills through interactions with other people, particularly caregivers) may be used for children and adolescents on the autism spectrum to improve core difficulties in social communication and social interactions. [EM3-4]

R 3.5 Early Intensive Behavioural Intervention (EIBI) may be considered to improve the development of adaptive skills and cognitive ability in children on the autism spectrum. It should be implemented by trained professionals and with sufficient intensity and be based on the intended goals for the child and family. [EM3-5]

R 3.6 Emotion Regulation Therapy (ERT) involves a range of treatment modalities (e.g., computer software programmes, videos, games) to teach emotion recognition, perception, and management skills, in children and adolescents on the autism spectrum, using a social pragmatic approach. ERT-based intervention may be considered for improving emotion recognition and socio-communication skills in children and adolescents on the autism spectrum. [EM3-6]

R 3.7 Naturalistic Developmental Behavioural Interventions (NDBIs) (a group of intervention practices that integrate behavioural and developmental theories, which are delivered in natural settings and use child-centred and motivation-based strategies to teach developmentally appropriate skills in the context of play and routine activities) may be used for children on the autism spectrum to improve social communication, language, cognitive, and play skills. [EM3-7]

R 3.8 Play-based intervention may involve the use of a variety of materials such as games, toys and activities to address play and social communication skills, while play-therapy is a non-directive approach that aims to address emotional and behavioural issues. These approaches may be used with children on the autism spectrum to improve language, joint-attention and social engagement skills, especially for those aged 12 years and below. [EM3-8]

R 3.9 Sensory integration therapy involving elements as described by Ayres may be recommended as a therapeutic intervention in children (3-12 years old) on the autism spectrum to improve functional and social participation outcomes. [EM3-9]

R 3.10 Sensory environmental modifications and sensory modulation strategies may be considered for selected children and adolescents on the autism spectrum to address their specific sensory needs. [EM3-10]

R 3.11 Weighted vests are not recommended for use as a therapeutic intervention in children and adolescents on the autism spectrum due to insufficient evidence for benefit, and potential for harm. [EM3-11]

R 3.12 Social skills intervention is recommended for children and adolescents on the autism spectrum to improve social communication and interaction skills. It can also lead to positive effects on challenging behaviours, adaptive and cognitive skills, and school and learning

skills. The social skills intervention should be customized to the individual's needs, preferences and environment. [EM3-12]

R 3.13 Visual supports (e.g., pictures, objects, written words, lists, schedules, choice boards) should be used for children and adolescents on the autism spectrum. [EM3-13]

CHAPTER 4: PHARMACOLOGICAL TREATMENT

R 4.1 Methylphenidate should be considered as the first line pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents on the autism spectrum. Any treatment plan should include non-pharmacological approaches. [EM4-1]

R 4.2 Atomoxetine may be considered for managing attention deficit hyperactivity disorder in children and adolescents on the autism spectrum if methylphenidate has been tried unsuccessfully or is contraindicated/not tolerated. [EM4-2]

R 4.3 Guanfacine may be considered for managing attention deficit hyperactivity disorder in children and adolescents on the autism spectrum after methylphenidate and atomoxetine have been tried unsuccessfully or if they are contraindicated. [EM4-6]

R 4.4 Risperidone and aripiprazole can be used for challenging behaviours (irritability and hyperactivity) in children and adolescents on the autism spectrum in the short term. There is insufficient evidence to conclude that risperidone and aripiprazole are beneficial in the long term (more than 6months). Both risperidone and aripiprazole can cause weight gain and somnolence. [EM4-4]

R 4.5 Selective serotonin re-uptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, sertraline, escitalopram, citalopram, paroxetine) should not be used for the treatment of core symptoms of autism in children and adolescents. SSRIs may be used to treat psychiatric conditions (e.g., anxiety, depression, OCD) in consultation with an appropriately trained specialist. [EM4-5]

R 4.6 Tricyclic antidepressants (TCAs) (e.g., clomipramine, tianeptine) should not be used for the management of challenging behaviours in children and adolescents on the autism spectrum. TCAs may be considered as a second- or third-line option to treat psychiatric conditions (e.g., depression) in consultation with an appropriately trained specialist. [EM4-6]

R 4.7 Anticonvulsants/mood stabilisers should not be routinely used for the management of challenging behaviours in children and adolescents with autism. They may be considered as a second- or third-line option to treat challenging behaviours or psychiatric conditions in children and adolescents on the autism spectrum, in consultation with an appropriately trained specialist. [EM4-7]

R 4.8 Mirtazapine should not be routinely used for the management of challenging behaviours in children and adolescents with autism. It may be considered as a second- or third-line option to treat anxiety in children and adolescents on the autism spectrum, in consultation with an appropriately trained specialist. [EM4-8]

R 4.9 Buspirone should not be used as an adjunct with risperidone for the treatment of challenging behaviours in children and adolescents on the autism spectrum. [EM4-9]

R 4.10 Celecoxib should not be used as an adjunct with risperidone for the treatment of challenging behaviours in children and adolescents on the autism spectrum. [EM4-10]

R 4.11 Galantamine should not be used as an adjunct with risperidone for the treatment of challenging behaviours in children and adolescents on the autism spectrum. [EM4-11]

R 4.12 Melatonin can be considered for sleep issues if there is no benefit from a psychosocial intervention. It should be used in conjunction with a psychosocial intervention and in consultation with a specialist trained in assessing and managing sleep issues in children and adolescents on the autism spectrum. [EM4-12]

R 4.13 Acamprosate should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-13]

R4.14 Amantadine should not be used for the treatment of core symptoms of autism in children and adolescents. Amantadine should also not be used as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum. [EM4-14]

R 4.15 Arbaclofen should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-15]

R 4.16 Based on current evidence, bumetanide should not be used for the treatment of core symptoms of autism in children and adolescents. Further results from clinical trials on bumetanide are awaited. [EM4-16]

R 4.17 D-cycloserine should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-17]

R 4.18 Memantine should not be used for the treatment of core symptoms of autism in children and adolescents. Memantine should also not be used as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum. [EM4-18]

R 4.19 N-acetylcysteine should not be used for the treatment of core symptoms of autism in children and adolescents. There is currently insufficient evidence for the use of N-acetylcysteine as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum and further studies need to be conducted. [EM4-19]

R 4.20 Riluzole should not be used for the treatment of core symptoms of autism in children and adolescents. Riluzole should also not be used as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum. [EM4-20]

R 4.21 Based on current evidence, intranasal oxytocin should not be used for the treatment of core symptoms of autism in children and adolescents. Further results from clinical trials on oxytocin are awaited. [EM4-21]

R 4.22 Balovaptan should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-22]

R 4.23 Insulin-like growth factor 1 (IGF-1; e.g., trofinetide, mecasermin) should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-23]

R 4.24 mTOR inhibitors (everolimus, rapamycin) should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-24]

R 4.25 Metformin should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-25]

R 4.26 Cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) should not be used for the routine treatment of core symptoms of autism in children and adolescents. There may be grounds for further well-designed clinical trials on galantamine for treating core symptoms of autism in children and adolescents. [EM4-26]

R 4.27 Cannabinoids should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-27]

R 4.28 Suramin should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-28]

R 4.29 Naltrexone should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-29]

R 4.30 Piracetam should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-30]

CHAPTER 5: EDUCATION AND TRANSITION

GPP 5.1 Parents and caregivers should consult appropriate professionals when considering educational interventions and school placement for their child on the autism spectrum, such as clinical and educational psychologists who are informed on the special educational provisions in Singapore. [EM5-1]

GPP 5.2 Professionals should be closely guided by Professional Practice Guidelines: Developmental and Psycho-educational Assessments and Provisions for Preschool-aged Children (2021) and Professional Practice Guidelines: Psycho-educational Assessment & Placements of Students with Special Educational Needs (2018) when advising parents on matters relating to education and transition. [EM5-1]

GPP 5.3 When making recommendations for appropriate educational intervention and school placement, professionals should take into account (i) the developmental needs of individual children, their preferences, strengths and special interests, (ii) family contexts, and (iii) the range of support and services available for Early Intervention and School-age provisions for children with developmental and/or special educational needs. [EM5-2]

GPP 5.4 Professionals should ensure that parents and/or caregivers are adequately supported to make informed decisions that can meet the longer-term educational needs, each child's preferences, strengths, and special interests, as well as the families' contexts. [EM5-2]

GPP 5.5 Professionals should engage in information sharing across agencies, if necessary, to ensure common understanding and to coordinate support for the child. [EM5-2]

GPP 5.6 Parent and/or caregiver engagement with regard to educational placement should be an ongoing process that is initiated as timely as possible, typically initiated as the child approaches 5 years old and/or is in Kindergarten 1. [EM5-2]

GPP 5.7 Professionals should assist parents to obtain a Comprehensive Needs Assessment for Transition Support for their children on the autism spectrum who are approaching school-going ages. [EM5-2]

GPP 5.8 Educators teaching students on the autism spectrum should be provided with knowledge and skills to provide reasonable accommodations and supports for these students in their classrooms. The depth/scope of information and mode of training should be adapted/customised to their specific teaching and learning context. [EM5-3]

GPP 5.9 School-based support provisions in mainstream schools should be based on the students' observed needs, and not solely on their diagnoses. [EM5-3]

GPP 5.10 School-based educational provisions offered to students on the autism spectrum should be determined by educational professionals working directly with the child, in consultation with parents, schools and when necessary, allied health professionals. [EM5-3]

GPP 5.11 Parents and caregivers should be referred to the MOE website for an up-to-date list of special education (SPED) schools that support students on the autism spectrum. [EM5-3]

GPP 5.12 Educational support for students on the autism spectrum with moderate-to-severe special educational needs in SPED schools should involve a multi-disciplinary team of specially trained teachers and Allied Health Professionals, as well as customised facilities to support teaching and learning. [EM5-3]

GPP 5.13 Specialised and individualised curriculum, guided by MOE's SPED Curriculum Framework, should be provided in accordance to each student's needs and ability. [EM5-3]

GPP 5.14 Professionals should ensure that transition support is systematically planned, holistic and person-centric; this includes having transition support differentiated based on the students' identified needs. [EM5-4]

GPP 5.15 Professionals should encourage and empower parents and caregivers to plan ahead and support their child to reduce the impacts of transitions; this includes advocating for the child, sharing information, and working closely with receiving schools. [EM5-4]

GPP 5.16 Professionals should provide families information about relevant support groups and organisations and recommended sources of information, as needed (i.e., taking into consideration family members' needs and contexts). [EM5-5]

GPP 5.17 When transitioning from preschool to formal schooling, children on the autism spectrum may benefit from explicit teaching and/or reinforced practices in the home and community in skills such as functional communication, emotional regulation, behavioural regulation, social, and adaptive skills. [EM5-6]

GPP 5.18 Professionals working with students on the autism spectrum who are transitioning within and across formal schooling settings (i.e., mainstream schools, specialised schools and SPED schools) should work alongside schools and parents to support the timely and accurate dissemination of relevant information with receiving school personnel. [EM5-7]

GPP 5.19 When transitioning to post-school pathways, students on the autism spectrum and their parents and/or caregivers should be provided information about the range of post-school options and the pre-employment and/or employment support. [EM5-8]

CHAPTER 6: COMPLEMENTARY AND ALTERNATIVE TREATMENT

GPP 6.1 Professionals should be prepared to discuss the evidence for Complementary and Alternative Medicine (CAM) with caregivers of children and adolescents on the autism spectrum. Shared decision-making on trials of CAM for autism is strongly encouraged between professionals and parents, so that the trials are time-based with clear objectives, outcome measures and endpoints. Parents and caregivers should not replace mainstream interventions with CAM. [EM6-1]

R 6.2 A gluten-free casein-free (GFCF) diet is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-2]

GPP 6.3 In children and adolescents on the autism spectrum, a healthy diet of a variety of fresh foods is recommended. Healthcare professionals should be equipped with information on recommended daily allowances of vitamins, minerals and other supplements for children and adolescents (appropriate to their age) and be able to discuss with parents possible benefits and harms of the various supplements and dosages. Intake of vitamins, minerals and probiotics in the form of natural fresh food should be encouraged. [EM6-2]

R 6.4 A ketogenic diet is not recommended as treatment for core symptoms of autism in children and adolescents. However, in children on the autism spectrum who have drug-resistant epilepsy, adoption of a ketogenic diet may be considered. A dietician should be involved in the management and monitoring of a child on a ketogenic diet. [EM6-3]

R 6.5 Camel milk is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-4]

R 6.6 Vitamin supplementation (of any type) is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-5]

R 6.7 Children and adolescents on the autism spectrum who exhibit symptoms suggestive of a vitamin, mineral, amino acid or other nutritional deficiency, should be evaluated, treated and monitored following appropriate clinical guidelines. [EM6-5]

R 6.8 Vitamin B6 is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-6]

R 6.9 Folinic acid is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-7]

R 6.10 Vitamin B12 is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-8]

R 6.11 Supplementation with zinc, magnesium, iron or any other minerals is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-9]

R 6.12 Amino acid supplementation is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-10]

R 6.13 Omega-3 fatty acids in any form or combination (including with phosphatidylserine) are not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-11]

R 6.14 Probiotics are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-12]

R 6.15 Secretin and digestive enzymes are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-13]

R 6.16 Sulforaphane is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-14]

R 6.17 Coenzyme Q10 is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-16]

R 6.18 Antimicrobial therapy should not be used in the treatment of core symptoms of autism in children and adolescents, as there is potential for harm, and no evidence of benefit. [EM6-16]

R 6.19 Microbial transfer therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-17]

R 6.20 Helminth therapy (in any type or form) should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-18]

R 6.21 Mesalazine is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-19]

R 6.22 Immunoglobulin therapy (in any form of administration) should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-20]

R 6.23 Stem cell therapy (in both intravenous and intrathecal forms) should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm. [EM6-21]

R 6.24 Hyperbaric oxygen therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-22]

R 6.25 Chelation therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-23]

R 6.26 Neurofeedback is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-24]

R 6.27 Vagal nerve stimulation should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-25]

R 6.28 Transcranial direct current stimulation is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-26]

R 6.29 Auditory integration therapy and other sound therapies are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-27]

R 6.30 Music therapy may be recommended as a complementary intervention approach for children and adolescents on the autism spectrum. Specifically, there is moderate level of evidence for an increased chance of global improvement, improved quality of life and reduced total autism severity. [EM6-28]

R 6.31 Dance movement therapy (DMT) is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-29]

R 6.32 Art therapy is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-30]

R 6.33 Vision therapy is not recommended as treatment for core symptoms of autism in children and adolescents. However, visual motor exercises may be considered for selected children on the autism spectrum who have visual difficulties as there is emerging evidence that such exercises have the potential to improve social communication and reduce repetitive behaviours. [EM6-31]

R 6.34 Aromatherapy should not be used as treatment for core symptoms of autism in children and adolescents, as there is potential for harm. [EM6-32]

R 6.35 Acupuncture is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-33]

R 6.36 Qigong massage or other types of massage are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-34]

R 6.37 Chiropractic, osteopathy and cranio-sacral therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm. [EM6-35]

R 6.38 Children and adolescents on the autism spectrum are recommended to engage in a variety of physical activities, at age-appropriate intensity and frequency, as indicated in the national physical activity guideline for children. [EM6-36]

R 6.39 Animal-assisted interventions are not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-37]

R 6.40 Mindfulness intervention is not recommended as treatment for core symptoms of autism in children and adolescents. However, it may be considered for selected children and adolescents on the autism spectrum to improve general wellbeing. [EM6-38]

R 6.41 Facilitated communication should not be used in the treatment of children and adolescents on the autism spectrum, as there is no evidence of benefit. [EM6-39]

CHAPTER 7: CO-OCCURRING CONDITIONS IN AUTISM

GPP 7.1 Children and adolescents on the autism spectrum should be followed up serially at spaced intervals in a holistic manner as they are at increased risk of academic, neuropsychological, adaptive challenges and certain medical conditions. Assessments and evaluations for these should be considered as needed when issues in these domains are identified. [EM7-1]

R 7.2 Children and adolescents on the autism spectrum presenting with academic challenges should be evaluated for their learning needs so as to guide parents and educators on further diagnostic assessments, interventions and support required, including access arrangements for learning. [EM7-1]

R 7.3 Professionals should be aware that children and adolescents on the autism spectrum may have significant delays in adaptive skills even in the absence of cognitive delays. Adaptive function should be assessed and monitored to support the functional needs of the child as indicated using standardised measures. [EM 7-2]

R 7.4 Professionals should be aware of the higher incidence of attention-deficit hyperactivity disorder (ADHD) among children and adolescents on the autism spectrum. In the presence of symptoms of ADHD, especially after the age of 5, prompt screening and referral for a thorough diagnostic evaluation using validated measures should be made to facilitate early management. [EM 7-3]

R 7.5 Professionals should be aware that children and adolescents on the autism spectrum are also likely to have motor difficulties. Formal screening for and diagnosis of developmental coordination disorder (DCD), using validated measures, should be undertaken in those with ongoing concerns for motor coordination and organizational skills beyond the preschool period. [EM 7-4]

R 7.6 Professionals should be aware of the need to assess for language, learning and other co-occurring developmental disorders in children and adolescents on the autism spectrum and support them accordingly. Caregivers would benefit from counselling regarding these co-occurring conditions and their potential impact on their child's learning and adaptive behaviour. [EM 7-5]

R 7.7 Children on the autism spectrum who have global developmental delay should be evaluated towards the end of the child's preschool period for the presence of intellectual disability. The diagnosis of global developmental delay should not be used when the child is past 5 years of age. [EM 7-6]

R 7.8 Children and adolescents on the autism spectrum with concerns for sensory processing difficulties, should be assessed via multiple modes of assessment including questionnaires, direct observations, and validated assessments, by an appropriately-trained individual, to facilitate a comprehensive evaluation. [EM 7-7]

R 7.9 Children and adolescents on the autism spectrum presenting with mental health symptoms (e.g., depression, anxiety) that impact on their daily functioning should be referred for further evaluation. Professionals should therefore have a high index of suspicion and be trained to look for co-occurring mental health issues in this group of individuals. [EM 7-8]

GPP 7.10 Professionals should be aware of the association between gender variance and autism. Children and adolescents on the autism spectrum who present with gender variance issues (where gender variance is an umbrella term used to describe gender identity, expression, or behaviour that falls outside of culturally-defined norms associated with a specific gender) may need further referral for evaluation and support for their social-emotional needs. [EM7-9]

R 7.11 Professionals should be aware of an increased prevalence of feeding and eating disorders among children and adolescents on the autism spectrum. These may be related to multiple factors including feeding dysfunction, sensory sensitivity, adaptive delays, behavioural issues and cognitive difficulties as well as pica (eating of non-food items), rumination (the process of regurgitating and re-chewing previously swallowed foods), obesity and food neophobia (fear of new foods) which should be evaluated for, as necessary. [EM7-10]

GPP 7.12 Children who are on the autism spectrum and have a history of persistent early-onset regulatory problems (defined as persistent problems with eating, sleeping and excessive crying beyond 3 months of age) may have a higher risk for feeding disorders and should be monitored for possible feeding and eating disorders. [EM7-10]

R 7.13 Healthcare professionals should be aware that children and adolescents on the autism spectrum have a higher occurrence of gastrointestinal conditions. Referrals for thorough evaluation should be made for those who present with persistent or recurrent gastrointestinal symptoms, such as colic or recurrent abdominal pain, vomiting, nonspecific diarrhoea, or constipation. [EM7-11]

GPP 7.14 Healthcare professionals should be aware that children and adolescents on the autism spectrum, with gastrointestinal disorders may present with atypical behavioural issues that may be indicative of acute abdominal conditions. Evaluation for the presence of a gastrointestinal disorder should be considered for children and adolescents on the autism spectrum who present with unexplained, persistent or sudden-onset atypical behavioural symptoms (such as head banging or increased stimulatory behaviours). [EM7-11]

GPP 7.15 Healthcare professionals should be alert to potential nutritional problems in children and adolescents on the autism spectrum. They should be monitored for their growth and nutritional status, in view of increased risk of metabolic and psychosocial complications related to being over or under weight. Referrals should be made as needed in the presence of poor growth or obesity. [EM7-11]

R 7.16 A complete audiological assessment is recommended in all children in whom there is a suspicion for autism so as not to delay the diagnosis of hearing impairment and subsequent management as needed in the event that hearing loss and autism co-exist. [EM 7-12]

GPP 7.17 There is an increased risk of obesity in children and adolescents on the autism spectrum, as differences in social interaction, challenges in motor coordination and psychosocial issues in autism can add to increased sedentary risks. Professionals should encourage prevention measures to reduce these risks, and monitor weight, height, body mass index and any significant changes in growth percentiles over time. [EM7-13]

R 7.18 Sleep difficulties are common in children and adolescents on the autism spectrum. Healthcare professionals should monitor sleep patterns and treat sleep dysfunction, as poor

sleep quality is associated with various negative consequences, including increased risk of being overweight and obesity. [EM7-13]

GPP 7.19 Healthcare professionals should be aware that there is an earlier onset of puberty, as well as an increased risk of precocious puberty, amongst girls on the autism spectrum as compared to neurotypical children. Routine surveillance, and referral for further evaluation should be done in the presence of symptoms or signs of concern. [EM7-14]

GPP 7.20 There is an increased incidence of visual problems (e.g., strabismus, refractive errors, anisometropia and amblyopia) amongst children and adolescents on the autism spectrum, which may present as unexplained behavioural issues or academic challenges. Routine vision screening and monitoring for visual problems, should be performed in these individuals and specialty referral be made as needed. [EM7-15]

GPP 7.21 Professionals should be aware that there is a higher incidence of cavities and gum disease amongst the children and adolescents on the autism spectrum, and these are associated with food selectivity and feeding issues. Routine dental screening and care should be facilitated, especially in the presence of untreated or undertreated cavities and gum disease in these individuals. [EM7-16]

CHAPTER 8: FOLLOW-UP AND PROGNOSIS

GPP 8.1 Interventions that promote positive parenting, mothering and fathering, should be encouraged. This should include support structures which help parents to understand their children/adolescent's autism and the associated challenges as early as possible. Parent training on how to respond to behaviours of concern and their participation in support groups should be encouraged. [EM8-1]

GPP 8.2 The focus of intervention for children and adolescents on the autism spectrum should address the holistic needs of these individuals across the entire lifespan. This includes addressing adaptive functioning and emotional wellbeing, in addition to academic achievement, in order to maximise the quality of life of the individual on the autism spectrum in the long run. The goals of the child/adolescent and his/her family should also be taken into consideration. [EM8-1]

GPP 8.3 Systematic transition planning should be encouraged for predictable major transitions for children and adolescents on the autism spectrum. Such transition planning should be proactive, holistic and person-centric. Of particular importance is the need for early transition planning for adolescents on the autism spectrum ahead of their graduation from mainstream or SPED school. [EM 8-1]

CHAPTER 9: CAREGIVER AND FAMILY SUPPORT

GPP 9.1 Professionals should be equipped with the understanding of how autism can affect caregivers and families in terms of social, economic, physical and mental health to support caregivers and families optimally. [EM 9-1]

GPP 9.2 Professionals should provide caregivers and family with information tailored to the child's/ adolescent's developmental age and needs and also support caregivers and families in accessing appropriate services for the child/ adolescent as well as caregivers. [EM9-2, 9-3, 9-4]

GPP 9.3 Professionals should strive to adopt a collaborative and family-centred approach in supporting caregivers towards optimal outcomes for a child/ adolescent on the autism spectrum, the caregiver and the family. [EM9-2, 9-3, 9-4]

GPP 9.4 Professionals should assess the emotional well-being of the caregiver and how the family is coping to provide necessary resources or support in the holistic care of a child and adolescent on the autism spectrum. [EM9-2, 9-3, 9-4]

GPP 9.5 Professionals should support caregivers and family during the child's/adolescent's transition across the lifespan, especially in terms of future care planning. [EM9-4]

R 9.6 Caregiver education and training programmes should be incorporated in intervention programmes for child and adolescents on the autism spectrum whenever possible as there is evidence to suggest positive effects on outcomes for both the child/adolescent as well as caregiver. [EM9-5]

CHAPTER 10: PROFESSIONAL TRAINING

GPP 10.1 Access to autism-related information should be provided for staff who interact with/care for children and adolescents on the autism spectrum (directly/indirectly). Extent and depth of information should be tailored to the specific professional's needs. [EM10-1]

FOREWORD BY DIRECTOR, CHILD DEVELOPMENT PROGRAMME, MOH

Caring for a person with autism spectrum disorder is a life-course endeavour and commitment. It entails a concerted and well-coordinated network of comprehensive medical care and inclusive educational support, forging a strong partnership with the parents and caregivers, in a receptive social environment. It amounts to setting up an intensive care ecosystem in the community. The vision is to ensure that these special children become contributing citizens who are valued by society.

Right up to the mid-1980s, autism as a neurodevelopmental disorder, classically described by Leo Kanner as "those who come into the world with an innate inability to form the usual, biologically provided contact with people" was an infrequently made diagnosis in our local children. One of the major contributions of the Development Assessment Clinic established in 1991, as a recommendation of the Advisory Council on the Disabled in 1988, was its attempt to appropriately recognise a group of children from those previously arbitrarily labelled as having mental retardation, speech and language delay, and behavioural and conduct disorders. With the availability of more specific and sensitive diagnostic tools, these children came to be identified as children with autism spectrum disorder (ASD), covering a wide range of functional capabilities from mild to needing high support.

With continued improvements in our developmental surveillance, screening and referral system, increased professional and public awareness, and revisions in the definitions of the condition, autism spectrum disorder currently accounts for between 20% and 25% of the 6,000-7,000 preschool children assessed at both child development departments at KK Women's and Children's Hospital and National University Hospital, under the Child Development Programme of the Ministry of Health, Singapore, in recent years.

Community-based multi-disciplinary early intervention programmes operated by various Social Service Agencies and funded by the Ministry of Social and Family Development (MSF), have been established across Singapore to bring the services close to the doorsteps of the families. These programmes evolved progressively into the current continuum of Developmental Support – Learning Support (DS-LS) and Early Intervention Programmes for Infants and Children (EIPIC). To minimise the impact on the parents and the caregivers, many family-centred programmes have also been initiated in the community to provide social supports, to empower and to strengthen the families. These national efforts were well evident in the three Enabling Masterplans from 2007 to 2022.

Singapore has a new vision towards building an inclusive society with a broader definition of meritocracy that entails recognising different strengths and different individuals. To achieve this, education is the key; and the education system must uphold this ethos, allowing the abilities of all Singaporeans to be fully developed. The government has started to invest heavily on pre-school education in the last decade, and education for children with special education needs has become compulsory in 2021. This next phase of changes in our education system must be integrated into and be complemented by an effective early childhood developmental and intervention programme, a nationwide family-centred supportive network of social and community services, and an efficient legal framework in child protection.

The first Clinical Practice Guidelines on Autism Spectrum Disorders in Preschool Children was published in March 2010, under the auspices of the College of Paediatrics and Child Health, Singapore (CPCHS), the Academy of Medicine, Singapore (AMS) and the Ministry of Health. Thirteen long years have passed, and the landscape has been fast-changing, with significant progress made in the various components of the evolving ecosystem. Therefore, the production of this revision cannot be more timely, so that all individuals involved can have a good understanding of their important roles and contributions in providing the best, seamless and hassle-free care to these children and their families. The Workgroup has further expanded its scope to include the entire child population, by including adolescents.

I would like to extend my heartfelt appreciation and congratulations to the hardworking Workgroup for a monumental task.

PROFESSOR HO LAI YUN

Director, Child Development Programme
Ministry of Health, Singapore
May 2023

FOREWORD BY PRESIDENT, COLLEGE OF PAEDIATRICS & CHILD HEALTH, SINGAPORE

Autism is characterized by varying difficulty with social interaction and communication, and the demands on the families and health care providers supporting and caring for them can be significant. Screening and diagnosing can be challenging, and identifying these children early is important as interventions from early childhood and across the life stages can optimize the development, health, and quality of life of the patients and their families. Early identification and timely access to early psychosocial interventions based on evidence can improve the ability of children on the autism spectrum to communicate and socially interact effectively. As the children grow, their abilities and needs, as well as that of their families will also evolve through their life stages. They may face challenges in education and eventually employment opportunities and may also have other co-morbidities which need to be managed.

In recent years, there is an overwhelming explosion of information regarding autism, many of which are myths and misconceptions, including interventions which are not evidence based and some which are even harmful to the children. The misinformation can delay diagnosis and prevent early intervention, and subject individuals to unnecessary or even harmful treatment.

Therefore, it is with great anticipation that the College of Paediatrics and Child Health present this clinical practice guidelines (CPG) for autism in children and adolescents, which is timely and will guide the community of healthcare providers, family caregivers, schools, government agencies and other stakeholders caring for these children, to recognize the standard of care and offer evidence-based interventions. This CPG will equip health professionals with evidence-based recommendations to provide holistic multi-disciplinary care of our children and adolescents on the autism spectrum and their families. This CPG recognizes the need to provide guidance to schools, and support for the families caring for these children, and also addresses the myriad of complementary and alternative treatment. Importantly it will provide a road map and framework for organizations devoted to caring for children and adolescents on the autism spectrum to review their current services and plan for the future.

On behalf of the College, I congratulate and thank the workgroup which has worked very hard to produce this document that will benefit our children and their families. I would also like to acknowledge and thank our donor Mrs Bernadette Khor (née Khoo Swee Lian) for her generous support.

PROFESSOR LEE YUNG SENG

President
College of Paediatrics & Child Health, Singapore
Academy of Medicine, Singapore
May 2023

GENERAL INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition that results in differences in social communication and social interaction, together with restricted, repetitive behaviours. These social communication and interaction differences, as well as restricted, repetitive behaviours, are also referred to as the 'core symptoms' of autism. It is also known as Autism Spectrum Condition (ASC), to reduce perceived negativity associated with the word 'disorder'. This terminology complements the neurodiversity movement, recognizes that autism is a brain/thinking difference, and that people with autism are different, not less. However, for the purposes of these guidelines, the formal diagnostic term of ASD will be used when referring to the formal diagnosis or its abbreviation. Elsewhere in this document, we use a combination of 'person first' language (e.g., children on the autism spectrum) as well as 'identity first' language (e.g., 'autistic children') to reflect the different preferences in terminology among those in the autism community, parents and professionals. Neurodiversity-affirming language has been used wherever possible, but in some instances, particularly to do with co-occurring medical conditions, terminology relating to a disorder may be difficult to avoid. The workgroup also acknowledges that autism is a lived experience and identity for many of those who are on the spectrum. These guidelines do not seek to cure autism but to improve services where possible.

The World Health Organization estimated the prevalence of autism in children to be approximately 1 in 160 in June 2021[1] although this varies greatly across different populations. The prevalence of autism in Singapore is estimated to be 1 in 150 of the population,[2] but the exact prevalence is unknown.

The severity and prognosis of autism is very variable between individuals, and the needs of affected individuals also evolve across the lifespan. There are also significant long-term demands placed on many caregivers, yet many individuals on the autism spectrum and their caregivers can cope much better with improved healthcare and community support. The majority of autistic individuals are diagnosed in childhood, hence the importance of having clear evidence-based guidelines focusing on this age group.

The first edition of the Academy of Medicine, Singapore – Ministry of Health (AMS-MOH) Clinical Practice Guidelines (CPG) on Autism Spectrum Disorders in Pre-school Children was published in 2010.[3] Since then, research within the field of autism has grown tremendously and, in turn, the number of publications in medical, psychological and educational literature pertaining to various aspects of autism has increased exponentially, giving rise to a need for updated guidelines that also cover a wider age range of children. Crucially, this literature needs to be evaluated in an open and unbiased manner and considered within the local context, so as to inform best practices to serve the needs of children in Singapore.

As a result, these updated guidelines, driven by the College of Paediatrics and Child Health (CPCHS), AMS, now also cover school-age children and adolescents, with new/expanded topics on Co-occurring Conditions, Education and Transition, Follow-up and Prognosis, and Professional Training.

OBJECTIVES AND SCOPE OF GUIDELINES

The primary objectives of these guidelines are to:

1. Promote effective healthcare for children and adolescents on the autism spectrum, by reinforcing good and evidence-based clinical practice, as well as to facilitate changes in professional practice that may not be consistent with current best practice.
2. Evaluate and apply evidence-based practices to use within the local Singapore context.

The guidelines are written to assist professionals who are involved in the surveillance, screening, diagnosis, intervention, and long-term management of children and adolescents on the autism spectrum; as well as for caregivers of these individuals. However, intervention and management of any child with autism still needs to be individualised depending on specific needs, and with input from experienced professionals who have sound knowledge of guideline recommendations.

Where other local professional practice guidelines (PPGs) or service development guidelines relevant to autistic individuals exist, such as those published by the Ministry of Education (MOE)[4,5] and Autism Resource Centre, Singapore (ARC(S)),[6] effort has been made to avoid duplication, and to cross-reference instead when appropriate.

TARGET POPULATION

The target population covered by these guidelines is children from infancy to adolescence, who have autism of any severity. In Singapore, the age of adulthood is defined as 21 years old. While some sections of these guidelines may mention adults or transitioning to adulthood, the scope is primarily focused on children. Where appropriate, special subgroups may have been given special attention, such as girls on the autism spectrum, racial or cultural differences, or socially-disadvantaged families.

TARGET USERS

The target users of the guidelines are all professionals caring for children on the autism spectrum in Singapore (e.g., primary care physicians, paediatricians, psychiatrists, nurses, psychologists, allied health professionals), as well as social workers, educators, caregivers, and community partners. The term 'professionals' is used when referring to all the above, whereas the sub-terms 'healthcare professionals' and 'educational professionals' are used in instances where these may be distinct. The intent is for the guidelines to be used to inform clinical decisions and inform standards of care for service development. This full guideline document will therefore have an accompanying executive summary and caregiver/lay version.

GUIDELINE WORKGROUP COMPOSITION

These guidelines were produced by a multi-disciplinary workgroup appointed by the CPCHS. The 22-member core workgroup comprised developmental paediatricians, psychiatrists, primary care physician, psychologists, allied health professionals, social worker, educators, early interventionists, and most importantly, caregivers of children on the autism spectrum. The workgroup members also represented public (i.e., KK Women's and Children's Hospital (KKH), National University Hospital (NUH), Institute of Mental Health (IMH)) and private healthcare sectors, the MOE, the National Institute of Education (NIE), and various social service agencies actively involved in supporting children on the autism spectrum (e.g., ARC(S), St Andrew's Autism Centre, Rainbow Centre, SPD). All workgroup members were sent terms of reference and submitted declarations of potential conflicts of interest prior to participation. A complete list of all workgroup members, their professional affiliations, roles in the CPG, as well as declarations of potential conflicts of interest, is provided in **Appendix 1**. None of the declared conflicts of interest were deemed to have influenced the guideline development process.

STAKEHOLDER SURVEYS TO IDENTIFY SERVICE GAPS IN SINGAPORE

The workgroup was unable to conduct a specific stakeholder survey on needs and experiences of caregivers and individuals on the autism spectrum in Singapore for the purposes of this CPG due to resource constraints. However in lieu of this, several existing sources of research/information on this subject were identified and reviewed in order to guide the clinical questions asked by the various sub-groups. The relevant extant literature from these sources is summarised below.

1. *An Autism Enabling Masterplan, by Autism Resource Centre (Singapore), January 2021*[6]
   A taskforce from the ARC(S), with the support of the Autism Network Singapore identified 6 high-need areas related to individuals on the autism spectrum in Singapore to set forth 14 key recommendations. These were formulated following consultation with approximately 500 individuals or families of individuals on the autism spectrum, with the aim of improving services, inclusion and care for members of the autism community. The recommendations covered several areas across the lifespan from childhood to adulthood. Specific high-need areas and gaps in care (relevant to children and adolescents) that were identified are as follows:

- Not all early intervention (EI) centres and preschools consistently deliver a curriculum that specifically meets the needs of young children on the spectrum
- There are insufficient numbers of qualified early childhood and EI professionals for those on the spectrum
- Students on the autism spectrum may not have their learning needs fully met through school curriculum and hours
- Continuing education of educators in autism tends to be limited with few professionals having the expertise to develop curriculum for students on the autism spectrum
- Evidence-based and evidence-informed best practices are not consistently practised by all educators in autism-specific special education schools
- Educators who receive training on special needs are typically not skilled enough to manage actual cases
- Number of Special Educational Needs Officers (SENO) available in each school may not be sufficient to meet students' needs
- SENOs may not currently receive adequate training to support students on the spectrum
- Learning supports for students on the spectrum are not systematically provided in institutes of higher learning settings
- The number of successful internships for students with autism may not be high due to either limited training and support to prepare them for internships and/or limited internship opportunities in industries
- Students on the spectrum tend to be under-prepared for work and living as adults.

2. *Understanding the Quality of Life of Children and Youth study by the National Council for Social Services (NCSS), 2022*[7]

This study by the NCSS was conducted between 2018 – 2019 and included a subset of children and youth with developmental needs (N=1537). This subset comprised of individuals aged 1 – 18 years with developmental disabilities including autism, but also attention-deficit hyperactivity disorder and specific learning disorders. The study survey was completed by face-to-face interviews with caregivers of these individuals although children older than 7 years of age were encouraged to respond directly. Key findings among children and youth with health/developmental conditions were:

- They had lower quality of life (QOL) scores than their peers without health/developmental conditions. Specifically, children and youth with health/developmental conditions reported lowest QOL facet scores in relying on friends, receiving and giving help to friends, and having enough money to do the same things as their friends.
- They faced challenges in the areas of independence and social inclusion due to their condition.
- Positive psychological well-being and social inclusion were the most important factors for their QOL.
- About a third (36%) of respondents expressed the need for additional services in terms of therapy, special interest groups and academic coaching services. Cost of service was the most frequently cited reason for not using the needed service, followed by inconvenient location, and lack of awareness or information about the service.

GUIDELINE DEVELOPMENT AND METHODOLOGY

The first workgroup meeting was convened on 21 June 2021. A working timeline was drawn up with the original aim to complete the draft of the main guideline document by December 2022. The key topics were defined, and subgroups created for every chapter of the guidelines. Workgroup members were assigned to different subgroups depending on their respective areas of expertise. Key PICO (Population, Intervention, Comparator, Outcome) clinical questions were drawn up within each subgroup, and are provided in **Supplement 1: Evidence Matrices**. Search strategies used key words from the respective PICO questions in the following electronic databases:

- CINAHL, Cochrane, Embase, Medline, PsycINFO, Proquest, PubMed, ScienceDirect, Scopus, Web of Science
- Grey literature databases, e.g., Google Scholar, Proquest, ClinicalTrials.gov, conference abstracts, dissertations/theses, surveys.

Search time period was pre-specified as January 2011 to current (2023), inclusive.

Search terms/strategies used are provided in **Supplement 1: Evidence Matrices**.

Existing Clinical Guidelines

In addition to these electronic databases, the following published guidelines on autism were independently reviewed and rated using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II)[8] Instrument by both guideline co-leads, using a Staged Appraisal approach with a focus on Domain 3 to achieve >70% as a priority, and >50% for Domains 1, 2, 4 and 6 as secondary requirements:

Asia Pacific

- Cooperative Research Centre for Living with Autism (Autism CRC), Australia. A National Guideline for the Assessment and Diagnosis of Autism Spectrum Disorders in Australia, 2018.[9]
- Cooperative Research Centre for Living with Autism (Autism CRC), Australia. National guideline for supporting the learning, participation, and wellbeing of autistic children and their families in Australia, 2022.[10]
- New Zealand ASD Guideline, 2016.[11]
- Ministry of Health, Malaysia. Clinical Practice Guidelines: Management of ASD in Children and Adolescents, 2014.[12]
- Indian Clinical Practice Guidelines for ASD, 2019.[13]

UK

- National Institute for Health and Care Excellence, UK. Autism: Recognition, Referral and Diagnosis of Children and Young People on the Autism Spectrum (CG128), updated December 2017.[14]
- National Institute for Health and Care Excellence, UK. The Management and Support of Children and Young People on the Autism Spectrum (CG170), updated June 2021.[15]
- Scottish Intercollegiate Guidelines Network, UK. Assessment, Diagnosis and Interventions for ASDs: A National Clinical Guideline (SIGN145), 2016.[16]
- British Psychological Society. Working with Autism: Best Practice Guidelines for Psychologists, 2021.[17]
- British Association of Psychopharmacology (BAP). ASD: Consensus Guidelines on Assessment, Treatment and Research, 2018.[18]

Europe

- European Society of Child and Adolescent Psychiatry ASD Working Party. ESCAP Practice Guidance for Autism: A Summary of Evidence-based Recommendations for Diagnosis and Treatment, 2021.[19]
- Autism Europe. People with ASD: Identification, Understanding, Intervention, 3rd Edition, 2019.[20]

USA

- American Academy of Pediatrics. Identification, Evaluation, and Management of Children with ASD, 2020.[21]

- American Academy of Child and Adolescent Psychiatry. Practice Parameter for the Assessment and Treatment of Children and Adolescents with ASD, 2014.[22]
- National Clearinghouse on Autism Evidence and Practice (NCAEP) Review Team, Frank Porter Graham Child Development Institute. Evidence-Based Practices for Children, Youth, and Young Adults with Autism Spectrum Disorder, 2020.[23]
- National Autism Centre, May Institute. Findings and Conclusions: National Standards Project Phase 2, 2015.[24]
- Missouri Autism Guidelines Initiative. ASDs: Guide to Evidence-based Interventions, 2012.[25]

Canada

- Canadian Paediatric Society, Autism Spectrum Disorder Guidelines Task Force. Position Statements on Early Detection for ASD in Young Children,[26] Standards of Diagnostic Assessment for ASD,[27] and Post-diagnostic Management and Follow-up Care for ASD, 2019.[28]

The AGREE-II ratings are provided in **Appendix 2: AGREE-II Ratings of Existing Clinical Guidelines**. It was determined that only four existing guidelines were of sufficiently high quality (Autism CRC Assessment and Diagnosis, NICE CG128, NICE CG170 and SIGN145) and these were used as references by the entire workgroup. The NCAEP and May Institute documents were systematic reviews instead of guideline documents. Of these, the NCAEP document was more recent and had a higher rating than the May Institute document, and was therefore recommended for reference.

Existing Systematic Reviews

In addition to the NCAEP systematic review above, the following have been considered in the development of these guidelines.

USA

- Agency for Healthcare Research and Quality, US Department of Health and Human Services. Therapies for Children with ASD: Behavioral Interventions Update, 2014.[29]
- Agency for Healthcare Research and Quality, US Department of Health and Human Services. Medical Therapies for Children with ASD: An Update, 2017.[30]
- Agency for Healthcare Research and Quality, US Department of Health and Human Services. Interventions Targeting Sensory Challenges in Children with ASD: An Update, 2017.[31]

Grading of Recommendation, Assessment, Development and Evaluation (GRADE)-like Process

In addition to considering the findings from the existing guidelines and systematic reviews listed above, other systematic reviews, meta-analyses, interventional and observational studies were also evaluated using the method of rating evidence and developing recommendations proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.[32] Key Recommendation (R) or Good Practice Point (GPP) statements were then derived from the evidence collated into an Evidence Matrix (EM), taking into account considerations of certainty and magnitude of effects, risk-benefit balance, cost-effectiveness, feasibility, stakeholder acceptability, and the context of prevailing legal and national policies in Singapore. Evidence that was not amenable to GRADE evaluation resulted in GPP instead of R statements. Both R and GPP statements hold similar importance in terms of implementation, with the main difference being the strength of evidence behind the statements.

Detailed Evidence Matrices (EMs) for each R or GPP statement are provided in **Supplement 1**.

Workgroup Consensus Surveys

Following the development of key R and GPP statements, all statements were then circulated internally to all 22 workgroup members for consensus rating on a scale of 1 (strongly disagree) to 9 (strongly agree), together with comments. The RAND/UCLA method was used to calculate a median score of

ratings, Interpercentile Range Adjusted for Symmetry (IPRAS) score, and a disagreement index. R and GPP statements that reflected disagreement or any consensus rating under 5 were discussed among all workgroup members to refine them further and revise as per feedback received. Statements that were revised were then put through further rounds of consensus survey voting until group consensus was obtained. Results of consensus surveys were incorporated into each EM to reflect original and revised statements where applicable.

External Review and Public Consultation

The final draft of the guidelines was then reviewed by a panel of independent external reviewers from Singapore and overseas, including autistic individuals and their caregivers, to obtain feedback. Comments were then taken into account in the formation of the final recommendations. The list of external reviewers and their affiliations is provided in **Appendix 1**.

The final draft of the guidelines was also published on the CPCHS website for a month for open consultation and public comments. Comments were also taken into account in the formation of the final recommendations. The detailed feedback from the public consultation and from external reviewers is provided in **Supplement 2: Public Consultation and External Reviews**.

Guideline Validity and Updating Procedure

These guidelines are valid for a period of 5 years, after which it is strongly recommended that a scoping review be conducted to evaluate for newer literature that might inform any significant changes in the recommendations.

GUIDELINE IMPLEMENTATION

Plans for Dissemination

The final complete guidelines, executive summary of recommendations, caregiver/lay version and all appendices will be made available on the CPCHS, Academy of Medicine Singapore's website for free download by the public.

News of the completed guidelines will be disseminated and the guidelines will be promoted via the following approaches:

- Formal launch of the guidelines at the 11th Singapore Paediatric and Perinatal Annual Congress (SiPPAC), which is the main annual paediatric conference in Singapore, widely attended by paediatricians and healthcare professionals from both public and private sectors, as well as from the region and further afield
- CPCHS Symposium, to cover the key recommendations and components of the guidelines, to be conducted in Singapore with an audience of healthcare professionals and personnel from early intervention centres, the education sector and relevant social service agencies
- Email broadcasts to all relevant stakeholders in the autism community through dissemination by the respective workgroup members who represent various disciplines and organizations within Singapore
- Email broadcasts to primary care healthcare professionals through CPCHS and the Chapter of Family Medicine Physicians, AMS
- Emails to local reviewers and individuals who gave feedback during the public consultation process
- Publication of the guidelines in the Annals, Academy of Medicine Singapore, which is a widely read, peer-reviewed, leading medical journal.

Potential Facilitators and Barriers to Implementation

Features which facilitate the implementation of the guidelines include the following:

- Special consideration to the local context, including but not limited to the availability of interventions and resources, cultural acceptability and local healthcare and educational systems
- Specific attention given to local literature where available to evaluate evidence for relevant clinical questions as they apply to Singapore
- The heterogenous composition of the workgroup with representatives from several sectors and institutions across the country, which allowed for recommendations to be considered from multiple perspectives and applied across disciplines and sectors
- The intentional incorporation of views of caregivers of individuals on the autism spectrum as part of the workgroup, expert reviews including those of autistic individuals, and public consultation with feedback on the content of the guidelines.

Potential barriers towards implementation of the guidelines include the following:

- Resource limitations (including, but not limited to, trained professionals, manpower, financial resources) within healthcare and educational organisations in the provision of care as per the guideline recommendations
- The time required to change established clinical processes, if needed, to match the recommendations described in the guidelines
- Limited availability of local literature specific to autism, especially for the majority of interventions examined
- The guideline is very comprehensive and hence its length may be a barrier to readability and prioritisation in implementation

Whilst all guidelines make recommendations towards best practice, enforcing the use of guidelines is limited unless additional efforts are made to do so nationally.

Cost-effectiveness was considered in all recommendations made in the guidelines, especially for those that involved a change from current clinical practices and with respect to provision of interventions. Availability of these interventions within the local context was also considered where applicable.

Suggestions for Implementation

Implementation of the recommendations laid out by these guidelines would be under the purview of each relevant organisation (e.g., healthcare, educational or community intervention agency). It is expected that the majority of the recommendations are in keeping with current practices, however, where differences in practice are present, the reason for these should be reviewed and addressed where possible.

Guideline Evaluation

Feedback should be actively sought by end-users of the guidelines from various organisations. This should include information on the acceptability and applicability of the recommendations and barriers, if any, to implementation of the recommendations.

Specific points for future audits and evaluations include the following:

- Quantifying changes in knowledge related to autism and the given recommendations among target users of the guidelines
- Adherence to recommendations within various professions and specific topics (e.g., investigations performed following a diagnosis of autism by physicians)
- Examining the use of complementary and alternative medicine among individuals on the autism spectrum and adherence to the published recommendations.

Appendices

- **Appendix 1:** Guideline Development Group and External Reviewers
- **Appendix 2:** AGREE-II Ratings of Existing Clinical Guidelines
- **Appendix 3:** Referrals for Autism Specialist Services in Singapore

Supplements

- **Supplement 1**: Evidence Matrices
- **Supplement 2:** Public Consultation and External Reviews

Abbreviations

AGREE-II, Appraisal of Guidelines for Research & Evaluation II; AMS-MOH, Academy of Medicine, Singapore – Ministry of Health; ARC(S), Autism Resource Centre, Singapore; ASC, autism spectrum condition; ASD, autism spectrum disorder; CPCHS, College of Paediatrics and Child Health; CPG, clinical practice guidelines; EI, early intervention; GPP, good practice point; IMH, Institute of Mental Health; IPRAS, Interpercentile Range Adjusted for Symmetry; KKH, KK Women's and Children's Hospital; MOE, Ministry of Education; NCAEP, National Clearinghouse on Autism Evidence and Practice; NCCS, National Council for Social Services; NIE, National Institute of Education; NUH, National University Hospital; PICO, population intervention comparator outcome; PPG, professional practice guidelines; QOL, quality of life; R, recommendation; SiPPAC, Singapore Paediatric and Perinatal Annual Congress; SENO, special educational needs officer.

CHAPTER 1: SCREENING AND DIAGNOSIS

This chapter covers key information and recommendations pertaining to the recognition, referrals and diagnosis of autism in Singapore. Early recognition of symptoms is essential for appropriate support to be implemented for children and their caregivers, and takes place via developmental surveillance and developmental screening.

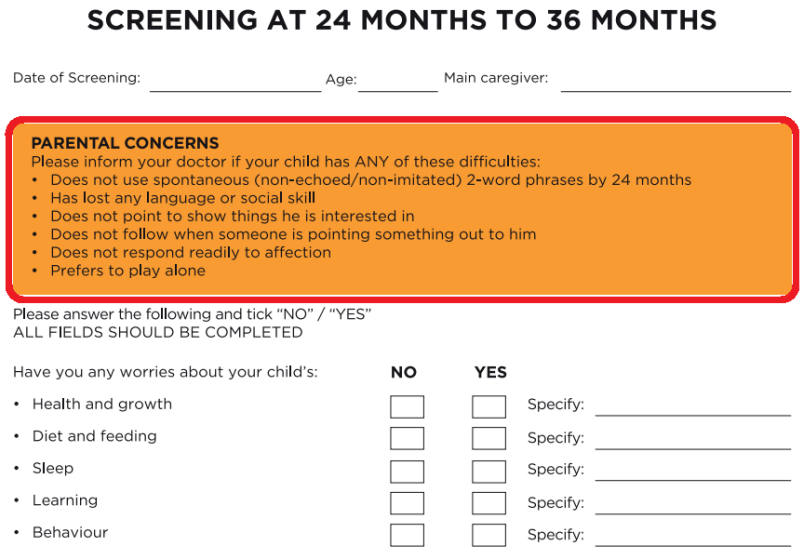
1.1 SURVEILLANCE

1.1.1 Definition of Developmental Surveillance

Developmental surveillance is an important technique used by paediatricians, defined as 'a flexible, continuous process whereby knowledgeable professionals elicit and attend to parental concerns, obtain a relevant developmental history, and perform skilled observations of children's development during the provision of health care across multiple time points'[33,34] Developmental surveillance should involve bidirectional communication with caregivers, early childhood educators, and interventionists, and be able to identify children at risk of developmental delays or disorders, in order to facilitate timely targeted screening, diagnosis, and intervention.[35]

In Singapore, very early developmental surveillance is largely conducted in the polyclinic (primary healthcare) setting, or by private family medicine or paediatric professionals. To aid the process, the Child Health Booklet published by the Health Promotion Board (HPB) provides developmental milestone checklists up to the age of 6 years, that tie-in with regular well-child visits for routine immunisations at preschool ages. To alert professionals, early signs of autism start to appear in coloured boxes at the top of each developmental screening checklist from the 6-month visit onwards. The checklists are designed for caregivers to check their child's development at any time. However, although approximately 90% of caregivers found the developmental screening checklists useful and easy to complete, 50% of parents only completed them during clinic visits or with professional help.[36]

Figure 1.1: Child Health Booklet developmental screening checklist and early signs of autism. Image used with permission from the Health Promotion Board, Singapore.



SCREENING AT 24 MONTHS TO 36 MONTHS

Date of Screening: _____ Age: _____ Main caregiver: _____

PARENTAL CONCERNS
Please inform your doctor if your child has ANY of these difficulties:
- Does not use spontaneous (non-echoed/non-imitated) 2-word phrases by 24 months
- Has lost any language or social skill
- Does not point to show things he is interested in
- Does not follow when someone is pointing something out to him
- Does not respond readily to affection
- Prefers to play alone

Please answer the following and tick "NO" / "YES"
ALL FIELDS SHOULD BE COMPLETED

Have you any worries about your child's:	NO	YES	
• Health and growth	☐	☐	Specify: _____
• Diet and feeding	☐	☐	Specify: _____
• Sleep	☐	☐	Specify: _____
• Learning	☐	☐	Specify: _____
• Behaviour	☐	☐	Specify: _____

In addition, regular well-child visits for routine immunisations are usually completed by the age of 18 months in Singapore. Hence, although attendance rates for the 18-month-old developmental surveillance visits are approximately 80%, this drops to about 25% for the 2-3 year and 4–6-year-old visits.[36] Yet these are critical periods during which ongoing surveillance for developmental delays is essential. In Singapore, approximately 90% of children are enrolled in preschools from age 4 onwards,[37] and even 69% of 3-year-olds are in a preschool. Preschools are therefore also ideal settings for ongoing

developmental surveillance, and as such, the Early Childhood Development Agency (ECDA) was launched in 2013 to facilitate this. Under the ECDA, the Development Support-Learning Support (DS-LS) Programme[38] provides developmental surveillance and on-site intervention for children with mild developmental delays in Kindergarten 1 and 2 (5 and 6 year olds). The programme is being reviewed to consider possible extension into Nursery 1 and 2 age groups (3- and 4-year-olds, Early Years pilot). To support the most socially and developmentally at-risk families, the ECDA also oversees the KidSTART programme,[39] which supports low-income parents at home, in the community and at preschools on developmental surveillance from birth to 6 years.

At the time of writing, there is no surveillance programme specifically for autism or mental health concerns in Singapore beyond the preschool age.

1.1.2 Early Identification of Autism

It is recognised that while there is substantial heterogeneity in the presenting features of autism, there are also early signs of autism that can be reliably detected at 12–24 months of age, although not yet reliable for children under 12 months old.[40] Developmental trajectories can also serve as possible indicators of autism. Although there is no direct evidence linking early identification of autism symptoms to improved long-term outcomes, the whole aim of early identification is to facilitate referral for early intervention. Early intervention of at least 6 months' duration has been shown to result in improved cognitive functioning (IQ), social communication, and adaptive functioning across different intervention types for a follow-up period of up to 9 years, indicating maintenance of treatment effect,[41–44] although more studies on long-term outcomes are warranted. There is a larger body of evidence on short-term improvements (See Chapter 3: Intervention).

GPP 1.1 ***Professionals should identify autism early, because early identification provides the opportunity for prompt referral and intervention, which may lead to improved long-term outcomes. [EM1-1]***

Effective developmental surveillance should take place over sequential and repeated visits as a child grows.[35,45] Early signs of autism may not always be evident in very young children,[46] and children with milder autism may present with more subtle symptoms,[47] or stereotypical behaviours may only become apparent at a later age. Signs of autism may also be missed in a brief, one-off consult, if further concerns from caregivers are not elicited or further developmental testing is not conducted.[48] Developmental surveillance programmes, in which community nurses are specifically trained on recognising early signs of autism to monitor very young children from 8–24 months old, have shown that accurate identification of autism can be achieved in a structured, sequential, repeated-visit developmental surveillance programme for the general population.[49] Factors associated with earlier diagnosis include greater symptom severity, higher socioeconomic status, and greater parental concern about initial symptoms, but geographic variations also exist.[50]

Additionally, studies have shown that caregivers may express concerns for symptoms of autism in children as young as 17–24 months of age,[51–54] but passive/reassuring healthcare provider responses could subsequently lead to longer delays in diagnosis.[54] Screening of high-risk children could improve detection to as early as 14 months,[55] and caregivers are more likely to act on early concerns if they receive appropriate support and specialist referrals from primary healthcare providers.[51] However, local studies show that in almost 20 years, healthcare professionals continue to have difficulties identifying signs of autism, and almost a third still practise a 'wait-and-watch' approach.[56,57]

Web-based developmental surveillance is an emerging option, but most studies have adopted specific screening tools and are therefore screening rather than surveillance programmes.[58] The evidence is currently limited on the utility of this although acceptability seems good.

Although there is no structured developmental surveillance programme beyond the preschool age in Singapore, healthcare and education professionals should remain vigilant for possible autism in any child or adolescent with ongoing difficulties relating to communication, social interaction, behaviour or

mental health. However, professionals should also still be aware that there may be other explanations for individual signs and symptoms.

GPP 1.2 ***Surveillance for early signs of autism should be embedded in a national developmental surveillance programme. [EM1-1]***

GPP 1.3 ***Developmental surveillance should be performed on several occasions at periodic intervals so that the signs of autism can be detected. [EM1-2]***

GPP 1.4 ***Caregivers' concerns about a child's communication, social interaction, play and behaviour should be elicited at every well-child clinic visit. Caregivers' attention should be drawn to the 'Parental Concerns' items in the Child Health Booklet, and they should be encouraged to inform healthcare professionals if their child shows any of these difficulties. [EM1-3]***

GPP 1.5 ***Preschool teachers' concerns about a child's communication, social interaction, play and behaviour should be elicited in preschool developmental surveillance programmes. [EM1-3]***

GPP 1.6 ***Professionals should initiate early specialist referrals for preschool children with concerns related to communication, social interaction, play or behaviour, instead of reassuring parents or adopting a wait-and-see attitude. [EM1-4]***

See **Appendix 3: Referrals for Autism Specialist Services in Singapore**

Recommendations on autism-specific screening (as opposed to developmental surveillance) are provided in Section 1.2.

Recommendations on training requirements for healthcare professionals involved in the surveillance, screening and diagnosis of autism are provided in Table 1.6 and Chapter 10: Professional Training.

Please also refer to the PPG on Developmental and Psycho-Educational Assessments and Provisions for Preschool-Aged Children jointly published by the MOE, MSF and ECDA in 2021[5] for further guidance with regard to preschool settings.

1.1.3 Early Signs of Autism

The early signs of autism include the following:

At 12 months of age:

- Little or no eye contact
- Lack of social smiling or shared excitement with a glance or smile
- Lack of babbling
- Little or no use of waving bye, reaching for hugs, pointing to needs, or holding up objects to show someone
- Little or no response to name being called.

At 18 months of age – <u>all the above and including</u>:

- No single words (e.g., mama, papa, bye-bye, etc.)
- Lack of imitation of actions (e.g., nursery rhyme actions) or words (e.g., trying to say a word when taught)
- Lack of interest in other children.

At any age:

- Avoidance of or difficulty maintaining eye contact
- Poor response to name being called
- Loss of previously acquired speech, babbling, or social skills (**regression**)
- Preference to be alone or play alone, or difficulty making friends
- Difficulty in sharing interests or enjoyment with others
- Difficulty in understanding other people's feelings, or reading their facial expressions
- Delayed speech and language development
- Repetitive language, echolalia (often repeating words or phrases when not meant to), excessive talking 'at' others, or unusual prosody of speech (monotonous or accented)
- Repetitive play, behaviours, or body movements
- Difficulties in adapting to changes in routines or environment
- Obsessions or extreme fixations on certain objects or topics
- Unusual reactions to the five senses (e.g., oversensitivity to sounds, tendency to stare closely at spinning things, tendency to sniff objects, etc.).

Regression (a loss or reduction) in language or social skills under the age of 3 years is a particularly strong predictor for autism. Research has indicated that approximately one-third of individuals on the autism spectrum experience some type of developmental regression, occurring at a mean of 1.78 years and equally among boys and girls.[59]

Studies from other Asian countries have reported that the critical or discriminating signs of autism may vary by race or culture. In Singapore, a study in siblings of children on the autism spectrum indicated that the most discriminating signs were difficulties following a point, lack of pretend play, lack of pointing, lack of spontaneous showing, poor response to name, lack of gaze following, and difficulties in understanding instructions.[60]

GPP 1.7 ***Children with one or more of the following clinical features should be referred promptly for comprehensive developmental evaluation [EM1-5]:***

- ***Any regression or loss of language or social skills***
- ***No babbling, use of gestures (waving bye, pointing), shared enjoyment (spontaneous showing, following point/gaze), or response to name by 12 months***
- ***No single words, following of instructions, or pretend play by 18 months***
- ***Lack of eye contact or social response, or any unusual repetitive, rigid, obsessive, or sensory behaviours at any age***

GPP 1.8 ***Professionals should remain vigilant for possible autism in any child or adolescent with ongoing difficulties relating to communication, social interaction, behaviour or mental health. [EM1-5]***

Table 1.1: Factors associated with increased likelihood of autism

Factors	OR/RR (95% CI)
History of autism in a sibling[61,62] - Childhood autism - ASD	 Adj RR 22.27 (13.09, 37.90) Adj RR 13.40 (6.93, 25.92)
Prematurity[63] - <35 weeks - <28 weeks	 Adj OR 2.45 (1.55, 3.86) Adj OR 2.5 (1.6, 3.9)
Birthweight <2500 g[64]	Adj OR 2.15 (1.47, 3.15)
History of neonatal hypoxic encephalopathy[64]	Adj OR 6.7 (1.5, 29.7)
Intrauterine exposure to maternal anti-epileptic medication[65]	

- Oxcarbazepine - Valproate - Lamotrigine - Lamotrigine+valproate	OR 13.51 (1.28 to 221.40) OR 17.29 (2.40 to 217.60) OR 8.88 (1.28 to 112.00) OR 132.70 (7.41 to 3851.00)
Paternal age[66] - 40–49 years - 50 years or older	 Adj OR 5.75 (2.65, 12.46) Adj OR 2.7 (1.5, 4.8)
Maternal age over 40 years[66]	Adj OR 1.51 (1.35, 1.70)
Parental history of mental health condition[63] - Schizophrenia-like psychosis - Affective disorder - Other mental and behavioural disorder diagnosis	 Adj RR 3.44 (1.48, 7.95) Adj RR 2.91 (1.65, 5.14) Adj RR 2.85 (2.20, 3.69)

Abbreviations: Adj, adjusted; ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio; RR, relative risk.

Table 1.2: Genetic syndromes associated with autism

Genetic Syndrome	**Prevalence of Autism**[67,68]
Rett syndrome	Female individuals only: 61%
Cohen syndrome	54%
Cornelia de Lange syndrome	43%
Tuberous Sclerosis Complex (TSC)	36%
Angelman syndrome	34%
CHARGE syndrome	30%
Fragile X syndrome	Male individuals only: 30%; mixed sex: 22%
Phosphatase and tensin homologue (PTEN) hamartoma syndrome	25%
Neurofibromatosis type 1	18%
Down syndrome	16%
Noonan syndrome	15%
Williams syndrome	12%
22q11.2 deletion syndrome (DiGeorge syndrome)	11%

Other candidate genes implicated in autism include *SLC25A12*, *OXTR*, *RELN*, *5-HTTLPR*, *SHANK*, *CNTNAP2* and *VDR*.[69]

The details on the strengths of risk factor associations are provided in Evidence Matrix 1-6 [EM1-6]. It is acknowledged that at the time of writing, some of the risk factors above have been more clearly associated with a child developing autism, than others. It is therefore likely that these lists of risk factors need to be reviewed as research progresses and more clarity is obtained.

GPP 1.9 ***Healthcare professionals should be aware of the factors associated with an increased likelihood for developing autism, and may consider targeted screening for children presenting with developmental concerns or these factors. Specific factors associated with increased likelihood of autism include:***

- ***History of autism in a sibling***
- ***Prematurity of <35 weeks' gestation or birth weight <2500g***
- ***History of neonatal hypoxic encephalopathy***

- ***Having a genetic syndrome known to be associated with autism***
- ***Intrauterine exposure to maternal anti-epileptic medication***
- ***Advanced parental age at child's birth (>40 years of age)***
- ***Parental history of mental health condition.***

[EM1-6, 1-9 and 2-2. Please see Chapter 2 (Sections 2.1 and 2.2) for additional information]

1.2 SCREENING

1.2.1 Definition of Developmental and Autism-specific Screening

Developmental screening refers to the use of brief, validated and standardised screening tools to identify children who require a comprehensive developmental evaluation for developmental delays/disorders, at specific time-points.[34,35]

Level I screening is conducted with the general population (i.e., an unselected group).[70] Level II screening is conducted with a selected population with a higher likelihood of autism, such as younger siblings of children on the autism spectrum, premature children, children with developmental concerns, and children with certain medical and genetic conditions.[71]

Numerous autism-specific screening tools have been developed across the past couple of decades. There are tools which require only professionals to make direct observations of the child, tools requiring only parents to provide their reports, and tools using a combination of both professional observations and parent report. The clinical utility and feasibility of each type of screening tool for a specific setting can depend on the amount of professional manpower available (to make those direct observations of the child), time required for completion of the screening tools, how it fits into the clinic process, and the ability of parents to respond accurately to the questions.

The performance of screening tools is described in terms of sensitivity, specificity, positive predictive value and negative predictive value. For autism-specific screening tools,

- Sensitivity indicates the proportion of all children on the autism spectrum who test positive with the screening tool. Sensitivity is an important value to examine for a screening tool, and values of above 0.70 are recommended.[72] An autism-specific screening tool should have a high sensitivity so that children who will benefit from further evaluation can be identified.
- Specificity indicates the proportion of all children not on the autism spectrum who test negative with the screening tool. Specificity is an important value for level II screening, and values of above 0.80 are recommended.[72] For children who have a high probability of the condition, it is important that the screening tool is able to further discriminate children who have a higher likelihood of being on the autism spectrum from those who do not.
- Positive predictive value indicates the proportion of children who tested positive with the screening tool who were eventually confirmed to be on the autism spectrum. A low positive predictive value would mean a high false positive rate.
- Negative predictive value indicates the proportion of children who tested negative with the screening tool who were eventually confirmed to be not on the autism spectrum. A low negative predictive value would mean a high false negative rate.

1.2.2 Level I Screening for Toddlers (Under the Age of 4 Years Old)

In the general paediatric population and toddlers under the age of 4 years old, the Modified-Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F) is the most well-studied tool.[73] Further details on the age that the M-CHAT-R/F is validated for and its performance, along with the characteristics of other autism screening tools are provided in Table 1.3.

A review of the currently available literature by Sanchez-Garcia et al. (2019),[74] suggests that while these autism-specific screening tools for toddlers have a pooled sensitivity of 0.72 (95% CI 0.61–0.81), there is very low certainty of evidence. Furthermore, positive predictive values across the autism-specific screening tools, with the exception of the Social Attention and Communication Surveillance (SACS),[75] have been found to be relatively low (~0.50). Due to the high false positive rates, which can potentially create unnecessary worry to parents and costs to the healthcare system, clinical practice guidelines in most countries still do not recommend the use of autism-specific screening tools universally to identify children who have a likelihood of autism. This is despite M-CHAT-R/F results indicating that most of the children who were identified as false positives on the autism-specific screening tools may also have other developmental delays.

SACS has a good positive predictive value of >0.80, but it is an observational tool administered by maternal and child health nurses, developed in Australia. It requires specialized training provided to the nurses and it may not be feasible to implement on a large scale in Singapore due to the specialised manpower required.

There is also a wide range of performance characteristics of the autism-specific screening tools across cultures and contexts. For example, the M-CHAT has been found to have lower sensitivity values when used in other cultures (e.g., 0.–5-0.65 in Inada et al. (2011) and 0.48 in Kamio et al. (2014) in Japan).[76,77]

When considering an autism-specific screening tool for toddlers, the M-CHAT-R/F will be the logical choice, as it is freely available in the public domain and the most well-researched autism-specific screening tool. The M-CHAT-R/F has also been used sporadically in Singapore's primary care setting. However, it is often used as a supplement to the clinical judgement of healthcare professionals on whether the children will benefit from further developmental evaluation and has not been used as the sole reason to indicate specialist referral or to exclude a diagnosis of autism.

1.2.3 Level I Screening for Children Above the Age of 4 Years Old

There is limited research of adequate quality on autism-specific screening tools for children above the age of 4 years old. For autism-specific screening of children 4 years old and older, the most well-researched tool – the Social Communication Questionnaire (SCQ) – requires additional cost and may not be easily available for use to most professionals. There are other tools that are freely available in the public domain, but their psychometric properties have not yet been examined for population screening.

A review of the currently available literature by Chesnut, et al.,[78] suggests that the SCQ is an acceptable screening instrument for autism (area under the curve = 0.885), but also indicates large inconsistencies across the studies in the reported sensitivity (range 0.47 to 0.96), and specificity (range 0.52 to 1.0). Further details on the age that the SCQ is validated for and its performance are provided in Table 1.3, along with details of other tools for children 4 years old and older.

Table 1.3: Psychometric properties of selected commonly-used autism-specific screening tools

Study	Screening tool	Country	Mode of administration/ Time taken	Sample size	Age range	Cut-off score	Sensitivity	Specificity	Cost
Robins et al. (2014)	M-CHAT-R/F	USA	Parent/Care-giver report, 5 to 10 mins	16,071	16 to <31 months old	≥3	0.85	0.99	Free
Barbaro et al. (2022)	SACS-R	Australia	Professional observation at 12-, 18- and 24-months (requires training)	13,511	11 to 24 months old	'Atypical' to 3 of 5 Key Items	0.62	1.00	Training costs
Chestnut, et al., (2017)	SCQ	USA	Parent/Care-giver report, 5 to 10 mins	1734 (subsample of children	>4 years old	≥15	0.69 – 0.96	0.54 – 1.00	Paid

Study	Screening tool	Country	Mode of administration/ Time taken	Sample size	Age range	Cut-off score	Sensitivity	Specificity	Cost
				>4 years old)					
Constantino & Gruber (2012)	SRS-2	USA	Parent/Care-giver or Teacher report, 15 to 20 mins	1,963	2.5 to 89 years old	≥60 (population screening)	0.92	0.92	Paid
Allison, et al. (2021)	Q-CHAT	UK	Parent/Care-giver report, 5 to 10 mins	3,770	18 to 30 months old	≥39 (population screening)	0.44	0.98	Free
Ehlers et al. (1999)	ASSQ	Sweden	Parent/Care-giver or Teacher report, 15 to 20 mins	110	6 to 17 years old	≥19 (Parent) ≥22 (Teacher) (clinical screening)	0.62 (Parent) 0.70 (Teacher)	0.90 (Parent) 0.91 (Teacher)	Free
Auyeung et al. (2008)	AQ (Child version)	UK	Parent/Care-giver report, 5 to 10 mins	1,765	4 to 11 years old	≥76 (general population and ASD sample)	0.95	0.95	Free
Einfeld & Tonge, 2005	DBC-ES	Australia	Parent/Caregiver report, 5 to 10 mins	120	18-48 months	≥11	0.83	0.48	Paid
Gilliam (2014)	GARS-3	USA	Parent/Caregiver report, 5 to 10 mins	Data not available	3 to 22 years	≥55	0.97	0.97	Paid

Note. *SRS-2* social responsiveness scale–second edition. *Q-CHAT* quantitative checklist for autism in toddlers. *ASSQ* autism spectrum screening questionnaire. *AQ* autism spectrum quotient (child version). *DBC-ES* developmental behaviour checklist–early screen. *GARS-3* Gilliam autism rating scale–third edition.

R 1.10 ***Based on current evidence, the universal use of autism-specific screening tools in the general paediatric population with no risk factors is not recommended. [EM1-7]***

R 1.11 ***Where there are concerns for developmental delay in children, the application of an autism-specific screening tool can supplement the clinical judgement of healthcare professionals but should not be used as the sole reason to initiate specialist referral or to exclude a diagnosis of autism. [EM1-7]***

GPP 1.12 ***Professionals who decide to implement the use of an autism screening tool should be aware of the performance characteristics (e.g., false positives, false negatives) and limitations of the tool, and that performance characteristics can vary across different cultures and contexts. [EM1-7]***

Autism-related behaviour differences can be observed in toddlers as young as 12 months old. Evidence however suggests that the accuracy of autism-specific screening tools for toddlers is better for older toddlers (i.e., estimated 21 months old and older) than for younger toddlers (i.e., 12 months old to 20 months old).

R 1.13 ***Autism-specific screening tools should be used within the age range for which they are validated. Professionals should be aware that the accuracy of screening tools has been found to be better for older toddlers (i.e., estimated 21 months old and older), than for younger toddlers (i.e., 12 months old to 20 months old). [EM1-8]***

1.2.4 Level II Screening for At-risk Paediatric Populations

There are several studies on screening tools for high-risk paediatric populations, but the quality of the research is very low to low. Some studies were also not able to provide performance characteristics due to the methodology adopted but provided evidence for high likelihood of autism in these populations. For example, Scarlytt de Oliveira Holanda et al. (2020) used the M-CHAT with preterm children and found that 50% showed early signs of autism.[79] Bradbury et al. (2020) used the M-CHAT-R/F with younger siblings of children on the autism spectrum and a low-risk sample and found that there were higher test-positive rates in the sibling group.[80]

Dudova et al. (2014) used the M-CHAT, Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist (CSBS-DP-ITC), and the Infant/Toddler Sensory Profile (ITSP) with preterm children.[81] Boone et. al. (2018) used the Brief Infant Toddler Social-Emotional Assessment (BITSEA) and the Pervasive Developmental Disorders Screening Test—II, Stage 2, Developmental Clinic Screener (PDDST-II-DCS), also with preterm children.[82] Both studies reported acceptable sensitivity (i.e., >0.70) for all the screening tools used.

There are two local studies which also found acceptable clinical utility for the M-CHAT and M-CHAT-R/F with high-risk samples. Koh et al. (2014) examined the use of the M-CHAT with children referred to a child development specialist clinic, and found acceptable performance characteristics for children in both the 18–30-month-old group and the >30-48-month-old group.[83] Wong et al. (2023), examining the use of the M-CHAT with younger siblings of children on the autism spectrum, found acceptable sensitivity, specificity and PPV values, in the 12-month-old age group [60] The performance of the M-CHAT-R/F declined at 18 months old and 30 months of age, although there is a possibility that parents reported less symptoms because some parents repeated the M-CHAT-R/F at the later age groups.

See earlier GPP 1.9.

1.2.5 Novel or Emerging Screening Methods

There is a growing area of research examining various neurophysiological and biochemical marker differences (e.g., eye-tracking, electroencephalogram, neuroimaging, auditory brainstem responses) in individuals on the autism spectrum versus those without. However, no single-mode or multimodal tool has been prospectively evaluated as a screening tool to date. As this is a rapidly expanding field of research, the evidence needs to be reviewed regularly as medical technologies, machine-learning, and artificial intelligence abilities develop.

GPP 1.14 ***Although research has found group differences in neurophysiological and other biomarkers between children on the autism spectrum and those without, these are not yet sufficiently developed to be accurate or reliable screening tools for autism. Based on current evidence, isolated neurophysiological and other biomarkers are not recommended for routine clinical use in screening for autism. [EM1-10]***

1.3 THE AUTISM DIAGNOSTIC PROCESS

The published mean ages of formal autism diagnosis in preschoolers in Singapore were approximately 3 years 10 months[84] in 2016, and 2 years 11.5 months in 2021[85]. A child suspected to be on the autism spectrum following an initial screening should be referred for specialist assessment. Diagnosis of autism spectrum disorder (ASD) is a complex process. It involves the extensive collection of information about the individual's developmental history and medical background; specific information about the individual's symptoms and behaviours relating to social communication, interaction, and atypical behaviours; and takes into account the wider contextual information relating to the family, environment and extant circumstances.

1.3.1 Diagnostic Classifications and Social Communication Disorder

There are currently two diagnostic classification systems in use for the diagnosis of autism spectrum disorder – the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR; Table 1.4)[86] and the International Classification of Diseases 11th Revision (ICD-11).[87] The current DSM-5-TR combines three independent diagnoses from the DSM-IV-TR – autistic disorder, Asperger syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS) – into a single diagnostic category of ASD, differentiated by different levels of symptom severity and support required. Specifically, autism is currently conceptualised as a condition with developmental differences in two core domains, i.e., social communication and social interaction, and restricted repetitive behaviours (RBBs) which can include restricted range of interests, activities and sensory challenges. The current ICD-11 classifies ASD as a neurodevelopmental disorder and an individual with this diagnosis is described as having 'persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour, interests or activities that are clearly atypical or excessive for the individual's age and sociocultural context'. The ICD-11 classification has also eliminated Asperger syndrome which was in ICD-10.

The diagnostic criteria to be used in the diagnostic process should be the current version of the DSM or ICD. Given the changes and revisions in the diagnostic systems over time with the emergence of new scientific evidence, the diagnostic classification system used should be clearly specified during the diagnosis process.

Table 1.4: DSM-5-TR criteria for Autism Spectrum Disorder *(terminology as per DSM-5 publication)*

DSM-5-TR Criteria for Autism Spectrum Disorder
To meet diagnostic criteria for ASD, a child must have persistent deficits in each of three areas of social communication and interaction (see A1 through A3 below) plus at least two of four types of restricted, repetitive behaviours (see B1 through B4 below): A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by all of the following, currently or by history: 1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions. 2. Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication. 3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers. B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history: 1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases). 2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day). 3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests). 4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behaviour. For either criterion, severity is described in 3 levels: Level 3 – Requires very substantial support, Level 2 – Requires substantial support, and Level 1 – Requires support.

C. 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).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger syndrome, or PDD-NOS should be given the diagnosis of autism spectrum disorder.

Specify if:

- 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 behavioural disorder
- With catatonia

GPP 1.15 ***Professionals involved in diagnosing autism in children and adolescents should use the current version of either the DSM or ICD, and should state which classification system was used. [EM1-11]***

With other studies reporting decreases in autism diagnoses made using the DSM-5 (2013), suggesting a more stringent diagnosis rubric compared to the DSM-IV-TR, there were concerns raised about children diagnosed with PDD using the DSM-IV criteria not meeting DSM-5 diagnostic criteria for ASD.[88–90] Nonetheless, the use of the DSM or ICD increases the reliability and validity of the diagnosis and should be used during the diagnosis process (SIGN145). Some local studies have compared the accuracy of diagnoses between the DSM-5 and DSM-IV or ICD. Wong and Koh (2016) determined that >90% of preschoolers diagnosed with autism on the DSM-IV-TR would still meet the DSM-5 criteria for ASD, which was higher than reported in other studies.[84] Sung et al. (2018) reported that in older children, the DSM-IV-TR performed slightly better, yielding a sensitivity of 0.946 and specificity of 0.889, compared to the DSM-5 (sensitivity = 0.837; specificity = 0.833).[91] Children with PDD-NOS were most likely to be misclassified on the DSM-5.

The DSM-5-TR and ICD-11 now include new diagnoses of social (pragmatic) communication disorder (SCD; DSM-5-TR) or pragmatic language impairment (ICD-11). These diagnoses arose from concerns raised by the DSM-5 workgroup as previously described, which may render such individuals ineligible for services despite having significant social communication and interaction differences. The DSM-5-TR criteria for SCD are given in Table 1.5. SCD should be considered in children and adolescents with social communication and interaction difficulties despite functional language, and who have no restricted, repetitive behaviours. Selected portions of these guidelines, especially interventions targeting social communication and interaction, will also apply to children and adolescents with SCD, although the primary focus of the guidelines is on autism.

Table 1.5: DSM-5-TR criteria for Social Communication Disorder *(terminology as per DSM-5 publication)*

DSM-5-TR Criteria for Social Communication Disorder
A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following: 1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context. 2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on the playground, talking differently to a child than an adult and avoiding use of overly formal language. 3. Difficulties following rules for conversation and story-telling, such as taking turns in conversation, re-phrasing when misunderstood and knowing how to use verbal and nonverbal signals to regulate interaction. 4. Difficulties in understanding what is not explicitly stated (e.g., making inferences). A non-literal or ambiguous means of language – for example, idioms, humour, metaphors, multiple meanings, which depend upon the context for the interpretation. B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement or occupational performance, individually or in combination. C. The onset of the symptoms is in the early developmental period, but the deficits may not become fully manifest until social communication demands exceed limited capacity. D. The symptoms are not attributable to another medical or neurological condition, or to low abilities in the domains of word structure and grammar and are not better explained by an autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay or another mental disorder.

GPP 1.16 ***Professionals involved in the diagnostic assessment of ASD should be aware that some children may not meet diagnostic criteria on the DSM-5-TR when they would have done so on the DSM-IV-TR. Some of these children may meet a diagnosis of Social Communication Disorder instead, and may still need interventions similar to those on the autism spectrum. [EM1-11]***

1.3.2 Multi-disciplinary and Single-clinician Diagnostic Approaches

Ideally, a multi-disciplinary approach involving trained professionals from different disciplines can provide a holistic and thorough examination of issues and concerns to be considered in the evaluation of autism.[92,93] Additional examination such as physical and neurological evaluation by a physician may be indicated to determine co-occurring conditions that may overshadow, overlap or account for the symptoms presented by the individual during the assessment. In younger children, auditory or visual examinations may be required to exclude treatable conditions. Extensive evaluations should, however, not be conducted routinely in view of invasiveness, lack of cost-effectiveness and low incidences of yield (See *Chapter 2, Section 2.4*).

GPP 1.17 ***Children being evaluated for autism should have (or be referred for) a medical examination, in order to facilitate a comprehensive evaluation and further medical treatment if needed. [EM1-12]***

Research evidence has demonstrated that the gold standard of an autism diagnosis would be a multi-disciplinary assessment whereby the evaluation is holistic, covers relevant aspects of an individual's functioning across different contexts, and is formulated based on the integration of all this information. The multi-disciplinary team may include developmental paediatricians, psychiatrists, psychologists, speech and language pathologists, occupational therapists, specialist educators and social workers. The multi-disciplinary team should comprise professionals with relevant training and expertise.[9]

GPP 1.18 ***A multi-disciplinary approach is recommended for the diagnosis of ASD in children and adolescents as far as practically possible, particularly in complex cases or cases where the single clinician determines that high diagnostic confidence cannot be achieved alone. [EM1-13]***

In consideration of efficiency and cost-effectiveness, children with clear autism symptomatology may be diagnosed by a single clinician.[94] Diagnosis of ASD should be conducted by a professional with relevant and appropriate training and expertise. It would still be recommended that the single professional be part of, or participates in, a consensus team diagnostic evaluation process with at least one other professional from another discipline or specialty.[9]

GPP 1.19 ***A single-clinician approach to the diagnosis of ASD may be considered when the following conditions are met: [EM1-15]***

- ***Conducted by specialist medical practitioners or psychologists with adequate training and experience in diagnosing autism in children and adolescents (see Table 1.6).***
- ***Include multi-source feedback from various settings in order to obtain a comprehensive picture of the child being assessed [EM1-16].***
- ***Include direct observation and interaction with the child being assessed.***
- ***Include thorough contemporaneous documentation on the child's symptoms of autism that meet the prevailing international diagnostic criteria for ASD (e.g., DSM-5-TR) [EM1-11].***

Table 1.6: Criteria for specialist medical practitioners or psychologists with adequate training and experience in diagnosing autism in children and adolescents

Criteria (Both 1 and 2 need to be met)	
1. Professional Qualification	Medical practitioners Specialist registration with the Singapore Medical Council in Paediatrics, Psychiatry, or Neurology *Or* Psychologists Registered or eligible to be registered with Singapore Register of Psychologists (SRP) AND holding a Master or Doctorate Degree in Clinical/ Neuro/ Educational Psychology that has a practicum component.
2. Clinical Experience in Autism Diagnosis	The professional should have at least 3 years of experience working in a multi-disciplinary team that conducts autism diagnostic assessments in order to have an understanding of the wide variation in presentation across the spectrum and of the normal variance in child development; how gender, cognitive ability, and other medical/genetic factors may affect presentation; and have adequate decision-making abilities to know when to refer a child on for multi-disciplinary team diagnoses instead. Having attended formal training on a validated autism-specific diagnostic tool would also be beneficial, as well as knowing when and how to use the tool appropriately.

The purpose of the diagnostic assessment should not only be to determine the presence or absence of autism, but also to encompass the following areas:

a. Review functioning in relevant domains
b. Identify needs and areas of intervention
c. Promote parents/ caregivers/teachers' understanding of the child
d. Identify areas of strengths and provide a holistic profile of the individual to facilitate intervention.

1.3.3 Diagnostic Information-gathering

An autism-specific developmental history is important to understand the reported behaviours in context. Autism-specific diagnostic tools can provide a useful framework to systematically elicit information about a child's current difficulties and developmental history. Some examples of autism-specific diagnostic tools are as follows (non-exhaustive list):

- **Autism Diagnostic Interview – Revised (ADI-R)**[95]
  The ADI-R is a standardised and structured parent interview which elicits information about a child's developmental history as well as information associated with the core symptoms of autism.
- **Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)**[96]
  The ADOS-2 is a standardised assessment which involves a semi-structured play or interview session determined by the age and communication level of the individual.
- **Diagnostic Interview for Social and Communication Disorders (DISCO)**[97]
  The DISCO is a semi-structured interview schedule used with the parent or carer of an individual to elicit a broad picture of the individual's behaviours and needs.
- **Childhood Autism Rating Scale, Second Edition (CARS-2)**[98]
  The CARS-2 is a behavioural rating scale used to interview parents to assess the prevalence and severity of autism in an individual.
- **Gilliam Autism Rating Scale, Third Edition (GARS-3)**[99]
  The GARS-3 is a norm referenced assessment tool used to indicate the prevalence and severity of the autism condition.
- **Developmental, Dimensional and Diagnostic Interview (3Di)**[100]
  The 3Di is a computer-based programme that utilises a decision-making algorithm when interviewing parents to diagnose autism and related disorders in children.

Studies have evaluated the accuracy of these instruments. While the ADI-R and ADOS have consistently demonstrated the strongest psychometric properties when used together, CARS and 3Di have also been reported to have high diagnostic accuracy. Randall et al. (2018) examined the use of these instruments in diagnosing autism in preschool children and reported significant variation in the sensitivity and specificity of the instruments, when compared to the gold standard evaluation process, i.e., a multi-disciplinary consensus approach.[101] The ADOS-2 may be more robust and present with highest accuracy, but does not account for the developmental history of the individual. The variability of the psychometric properties of these instruments across studies indicates that there is inconsistent or inadequate evidence for each of these instruments to be used on its own in the diagnostic process in comparison to the DSM criteria and multi-disciplinary approach.[102–107] The quality of evidence of the effectiveness of these tools to diagnose autism across the ages is still limited. While these instruments can be useful and assist in the collection of important information for diagnosis, it is not recommended that autism-specific diagnostic instruments be used to substitute clinical evaluation and diagnostic decision making via the multi-disciplinary approach.

R 1.20 ***Assessment and diagnosis of ASD should not solely rely on autism-specific diagnostic instruments, but should encompass a holistic profile of the child including developmental, medical, and social history, physical examination, consideration of differential diagnoses and co-existing conditions, cognitive, sensory, academic and adaptive behaviour profiles, as well as strengths, skills and needs to facilitate management plans. Autism-specific diagnostic instruments can complement the assessment process and supplement clinical observation and information collection. [EM1-14]***

Obtaining a history of a child's social and communicative behaviour does not substitute for direct observation, and assessments should be done through direct interaction with the child. Professionals need to have substantial training and experience to carry out such observation and evaluation of relevant behaviours.

Increasingly, researchers have adapted assessment tools to obtain clinical and behavioural information of the individuals, especially in situations whereby it may be difficult to conduct direct observation of or interaction with the individual.[108,109] Information obtained via telehealth observations or video-recordings may complement and enhance the information collected via the multi-disciplinary assessment, with minimal risk or harm involved to the child. This might be particularly useful in other countries to facilitate remote assessment of children in rural areas. However, in the Singapore setting, telehealth observations or video recordings may be considered as a substitute source of clinical information only in extenuating circumstances where direct observations of a child are not possible. Other forms of information collection such as surveys and feedback about the individual's functioning in their natural community and environment would be useful.

GPP 1.21 ***Information gathered to make a diagnosis should include reports on or observations of the child in the home, community or outside the clinic setting. [EM1-16]***

Information about the child's functioning from as many sources as possible outside the clinical setting can be considered.[16] This information can provide an enriched understanding of the individual in their natural environment which can further elucidate and clarify the diagnosis of ASD. This information could also be useful to reconcile discrepancies in observations or information collected in clinical settings or across different settings. The collection of this information can increase the confidence of the caregivers and parents in accepting the outcomes or findings of the assessment and further provide information that can facilitate and guide intervention.

1.4 OTHER DIAGNOSTIC CONSIDERATIONS

This section serves to highlight only some of the heterogeneity seen in autism, which is not only in the aetiology, neurobiology, onset, and course of core clinical autism symptoms but also in presentation amongst different genders, cultures and levels of cognitive functioning.[40] The diagnosis of autism can be more challenging in those at both extremes of cognitive ability. Other heterogeneity in the rates of language development, adaptive functioning, and co-existence with other disorders is covered in Chapter 7.

1.4.1 Autism in Girls

Traditionally, the prevalence of autism has been higher in boys than girls. However, there is now an increased recognition that girls and women on the autism spectrum may have often been misdiagnosed or underdiagnosed.[110] In a systematic review by Lockwood, Milner, Spain and Happe (2021),[111] the symptoms that differ between the two genders can be categorised into 6 areas: behavioural problems; social and communication abilities; language; relationships; restricted and repetitive behaviours and interests; and other additional diagnoses/difficulties.

Girls/females on the autism spectrum often go underdiagnosed for several reasons and this may include:

1. *Different presentation*: Females on the autism spectrum may present differently than boys and men with autism. For example, they may have better mimicry of social skills and may be more socially motivated, with better language and imaginative play, making their autism less noticeable (also known as masking).[110] Their restricted interests also tend to involve people/animals rather than objects/things, which may be less recognized as related to autism.
2. *Co-occurring concerns*: Females on the autism spectrum are more often diagnosed with other mental health concerns prior to being diagnosed with autism.[112]
3. *Awareness*: Traditionally, autism is believed to mostly affect males, hence healthcare providers may tend to overlook the possibility of autism in females. Consequently, healthcare providers may not be adequately attuned to the presentation of autism in females, hence leading to under- or misdiagnosis.

GPP 1.22 ***Professionals involved in the diagnostic process should consider that females on the autism spectrum may present with a different symptom profile and level of needs as compared to males with autism. [EM1-17]***

1.4.2 Cultural Considerations

Cultural differences and bias can affect an individual's diagnosis of autism. This is particularly so for individuals from a different cultural background. Research suggests that cultural and linguistic differences can lead to underdiagnosis of autism in minority populations.[113]

An assessment for autism is carried out when an individual is observed and reported to be facing persistent challenges in the area of social communication and interaction and restricted and repetitive behaviours (RRBs). Reports and observations are usually made by parents/caregivers and teachers; these reports and observations are bound by social customs, norms and rules that may differ between different cultural groups.

The ways in which parents share their initial concerns about their child's development may alter the next course of action as the type of screening and assessments which healthcare professionals would administer may differ. For example, some cultures may view autism traits, such as difficulty with social interactions, as normal behaviour and attribute it to the child being shy or being an only child and hence may not recognise them as part of a disorder.[114] Subsequently, interventions would also differ given that autism assessments rely heavily on parental reports, and interventions for children on the autism spectrum are targeted at their specific difficulties.

In the assessment of autism, it is also crucial for the professional to be aware of the professional's own cultural lens, as well as the patient's cultural background and their beliefs.

GPP 1.23 ***Professionals should be aware of cultural differences when assessing for autism. Understanding these cultural variations in appropriateness of behaviour would help the professional to cater their assessment to patients from different cultural backgrounds. [EM1-18]***

1.4.3 Autism and Intellectual Disability

The clinical features of autism and intellectual disability (ID) tend to overlap,[115] hence diagnosing autism in individuals with ID can be challenging. The symptoms of autism may be masked or difficult to distinguish from those of the ID itself.

Both conditions overlap in the areas of:

1. Difficulties with social interaction and behaviour (e.g., a lack of interest in socializing with others, disinhibition and inappropriate oversharing of personal information)
2. Difficulties in understanding social cues
3. Repetitive behaviours and fixated interests (although studies have shown that restricted interests or repetitive behaviours best differentiated between the two groups).

It is important for professionals to note that diagnosing autism in individuals with ID requires a holistic and individualised assessment, taking into account the unique needs and abilities of each person. A team of professionals, including psychologists, psychiatrists, and developmental specialists, may be required in the diagnosis of and intervention for individuals with ID and autism.

GPP 1.24 ***Professionals should be aware that there are overlapping features between intellectual disability (ID) and autism when assessing for autism in individuals with an intellectual disability. Autism should not be diagnosed if symptoms are better accounted for by ID. [EM1-19]***

Abbreviations

3Di, Developmental, Dimensional and Diagnostic Interview; ADI-R, Autism Diagnostic Interview – Revised; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; BITSEA, Brief Infant Toddler Social-Emotional Assessment; CARS-2, Childhood Autism Rating Scale, Second Edition; CI, confidence interval; CSBS-DP-ITC, Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist; DISCO, Diagnostic Interview for Social and Communication Disorders; DS-LS, development support-learning support; ECDA, Early Childhood Development Agency; GARS-3, Gilliam Autism Rating Scale, Third Edition; HPB, Health Promotion Board; ICD, International Classification of Diseases; ID, intellectual disability; ITSP, Infant/Toddler Sensory Profile; M-CHAT-R/F, Modified-Checklist for Autism in Toddlers, Revised with Follow-up; PDD-NOS, pervasive developmental disorder-not otherwise specified; PDDST-II-DCS, Pervasive Developmental Disorders Screening Test—II, Stage 2, Developmental Clinic Screener; RBBs, restricted repetitive behaviours; SACS, Social Attention and Communication Surveillance; SCD, social (pragmatic) communication disorder; SCQ, Social Communication Questionnaire; TSC, tuberous sclerosis complex.

CHAPTER 2: AETIOLOGY AND INVESTIGATIONS

Autism is a developmental disability that can cause significant social, communication and behavioural challenges. There are many factors that make a child more likely to develop autism and these include genetic, biological and environmental factors. Although there is a high degree of heritability of autism in twins, the concordance is not 100%, suggesting that biologic or environmental factors also play a part. In a majority of cases, the cause is multi-factorial and may be the result of complex interaction between the genetic, biological and environmental factors in an individual.

2.1 GENETIC FACTORS IN THE AETIOLOGY OF AUTISM

Family studies show that autism is highly heritable, with an increased recurrence risk of autism among children born to families where there is already a family member with autism. Evidence for the genetic basis of autism was based on concordance studies, in which the likelihood of developing autism was higher in monozygotic (60-92%) than dizygotic (0-10%) twins.[116–118] Large population-based cohort studies in Sweden, Denmark, California, Israel, Finland and Western Australia showed that the likelihood of developing autism rose with increasing 'genetic relatedness', being highest amongst monozygotic and dizygotic twins, followed by full siblings, maternal half-siblings, paternal half-siblings and cousins, in that particular order, as compared to the general population.[119,120]

Hansen et al. (2019) published a multi-national population-based study of livebirths from 1998 to 2007 who were followed through 2011 to 2015.[61] Participants were monitored for an autism diagnosis in their older siblings or cousins (exposure) and for their own autism diagnosis (outcome). Compared to the probability in unaffected families, there was a 8.4-fold increase in the likelihood of developing an autism spectrum disorder (ASD) following an older sibling with ASD, and a 17.4-fold increase in the probability of childhood autism following an older sibling with childhood autism.[61]

Autism has been associated with single gene disorders, copy number variants, chromosomal re-arrangements and various syndromes. Single nucleotide variants in hundreds of genes have been identified as potential causes for autism and may be inherited or may arise *de novo* (i.e., the disorder appears in the child but not in either parent).[21] It was estimated that the contribution of rare inherited and *de novo* genetic variants to autism was 2.6% and 9.5% respectively, based on twin and familial studies.[858]

Table 2.1 below summarises the clinical features, complications, genetic abnormalities and modality of testing of commoner genetic disorders associated with secondary autism. They include Fragile X syndrome, Angelman/Prader-Willi syndrome, Tuberous Sclerosis, Rett syndrome, PTEN Hamartoma syndrome and Down syndrome.

***Table 2.1*: Genetic disorders commonly associated with autism**

Syndrome	Genetic Abnormality	Clinical Features	Complication	Genetic Test	Inheritance
Fragile X syndrome[122]	CGG trinucleotide repeat expansion in *FMR1* on Chr X	Frontal bossing, long jaw, large testicles, delayed milestones (symptoms in males more than females)	Learning and intellectual disability	CGG trinucleotide repeat expansion analysis in *FMR1* gene	X-linked
Angelman syndrome[123,124]	Maternal 15q11-q13 deletion, Paternal uni-parental disomy, imprinting	Distinctive craniofacial features, delayed milestones, feeding difficulty	Seizures, sleep disorders, obesity	DNA methylation analysis, DNA sequencing and deletion/	Most cases are due to *de novo* genetic alteration with a very low risk of recurrence; Rarely,

Syndrome	Genetic Abnormality	Clinical Features	Complication	Genetic Test	Inheritance
	defect of maternal 15q11-q13 region, pathogenic variant in maternally derived *UBE3A*			duplication analysis of UBE3A gene	imprinting pattern of autosomal dominant inheritance, unbalanced translocation, non-disjunction
Tuberous Sclerosis[125]	Heterozygous pathogenic variant in *TSC1* (Chr 9) or *TSC2* (Chr 16)	Ash-leaf macules, facial angiofibroma, shagreen patch, subungual fibromas, seizure	Brain tubers, cardiac rhabdomyoma, renal angiomyolipo-ma	DNA sequence analysis of *TSC1* and *TSC2* genes	Autosomal Dominant
Rett syndrome[126]	Heterozygous pathogenic variant in *MECP2* (Chr X) (females)	Hand stereotypies, (especially flapping, wringing), drooling, hypotonic facies	Sleep disruption, eating difficulty	DNA sequence analysis of *MECP2* gene	X-linked (affected males have severe neonatal-onset encephalopath y)
PTEN Hamartoma syndrome[127]	Germline heterozygous pathogenic variant in *PTEN* suppressor gene	Macrocephaly (head circumference >2.5 SD above the mean) in 94%	Increased cancer risk (breast, kidney, thyroid, colon, endometrium)	DNA sequence analysis of *PTEN* gene	Autosomal Dominant-
Down syndrome[121]	Trisomy of Chr 21	Epicanthic folds, slanted palpebral fissures, short fingers and toes, brachycephaly, hypotonia, delayed milestones	Congenital cardiac disorders, intellectual disability	Karyotype	Non-disjunction, Unbalanced translocation, Mosaicism; Risk increases with maternal age

Note: chr = chromosome

GPP 2.1 ***Healthcare professionals should be aware of the strong genetic heritability of autism and monitor for features of autism in children who have siblings and/or first-degree relatives on the autism spectrum. [EM2-1]***

GPP 2.2 ***Healthcare professionals should be aware that some genetic conditions or syndromes may be associated with autism and should monitor the affected child for features of autism. Examples of genetic conditions or syndromes include Fragile X syndrome, Angelman syndrome, Tuberous Sclerosis, Rett syndrome, PTEN Hamartoma syndrome and Down Syndrome. [EM2-1]***

2.2 BIOLOGICAL FACTORS IN THE AETIOLOGY OF AUTISM

Numerous prenatal, perinatal and postnatal factors were evaluated in epidemiologic, population-based cohort and case-control studies to determine those associated with an increased likelihood of developing autism. Amongst them, some factors that appeared to be more consistently associated with an increased likelihood of developing autism were advanced paternal/maternal age (>40 years of age) at the time of the child's birth, male gender, prematurity (<35 weeks), low birth weight, and hypoxic ischemic encephalopathy at birth.[66,128–132] In practically all published reports, the prevalence of autism

was consistently higher among boys than girls, in a 4:1 ratio.[133,134] Studies published from Singapore also showed that the male:female ratio in young children is approximately 4.5:1.[84,135] However, systematic reviews and meta-analyses have not uncovered any *single* prenatal, perinatal or postnatal factor that was conclusively associated with an increased probability of autism in the offspring.

Several studies have suggested that maternal medication use may be implicated in the development of autism in their offspring, since the medications presumably reach the unborn foetus via the placental circulation. The medications studied included paracetamol, anti-epileptic monotherapy (such as sodium valproate and topiramate) and anti-epileptic dual-therapy medications (such as levetiracetam with carbamazepine, and lamotrigine with topiramate) and epidural analgesia for mothers in labour. Overall, there was insufficient evidence to support an association between maternal paracetamol ingestion and the development of autism in the offspring.[136–144] While maternal valproate usage was associated with the subsequent development of autism in the offspring,[145] the underlying biological mechanism and dose-response relationship remain unclear. The certainty of evidence regarding the association between maternal anti-epileptic therapy and autism is low because of 'confounding by indication', where the development of autism may be associated with the epilepsy itself rather than its treatment. Further large-scale epidemiologic studies are needed to answer these research questions. Also, as indicated previously in Chapter 1, Table 1.1, advanced parental ages and parental history of mental health conditions are also associated with increased likelihood for their children being on the autism spectrum.

Comprehensive review of the evidence related to potential biologic factors for the aetiology of autism have informed the following Good Practice Points:

GPP 1.9 ***Healthcare professionals should be aware of the factors associated with an increased likelihood for developing autism, and may consider targeted screening for children presenting with developmental concerns or these factors. Specific factors associated with increased likelihood of autism include:***

- ***History of autism in a sibling***
- ***Prematurity of <35 weeks' gestation or birth weight <2500g***
- ***History of neonatal hypoxic encephalopathy***
- ***Having a genetic syndrome known to be associated with autism***
- ***Intrauterine exposure to maternal anti-epileptic medication***
- ***Advanced parental age at child's birth (>40 years of age)***
- ***Parental history of mental health condition.***

[EM1-6, 1-9 and 2-2. See Chapter 1 (Sections 1.1.3 and 1.2.4) also]

GPP 2.3 ***Healthcare professionals should be aware that there is insufficient evidence for any association between maternal ingestion of paracetamol during pregnancy and the probability of autism in their offspring. Pregnant mothers do not need to avoid paracetamol ingestion in pregnancy if it is indicated. [EM2-3]***

GPP 2.4 ***Healthcare professionals should discuss the indications and side-effects of various anti-epileptic medications with pregnant women requiring such treatment, because there is evidence linking certain types of maternal anti-epileptic medication (especially sodium valproate) in pregnancy with the probability of developing autism in their offspring. [EM2-4]***

GPP 2.5 ***Healthcare professionals should be aware that there is insufficient evidence for any association between the use of epidural analgesia for labour/delivery in women and the probability of autism in their offspring. Pregnant mothers in labour do not need to avoid epidural analgesia if deemed necessary. [EM2-5]***

2.3 ENVIRONMENTAL FACTORS IN THE AETIOLOGY OF AUTISM

Due to incomplete concordance in monozygotic twins, it is now believed that environmental factors play a role in the development of autism. The mechanism underlying the autism aetiology is most likely polygenic, with environmental factors interacting with genetic factors to increase the probability.

Many reports worldwide have attempted to link various environmental factors or toxins with an increased likelihood of developing autism. These include childhood vaccinations usually recommended as part of the national childhood immunisation schedule, as well as exposure to heavy metals in the environment.

Comprehensive review of the evidence relating to autism and vaccinations[146–154] as well as heavy metal exposure[153,155–160] informed the following key findings and associated Good Practice Points:

GPP 2.6 ***Parents should be reassured that childhood vaccinations are not associated with autism, and should proceed with their child's vaccination schedule as recommended on the National Immunisation Schedule. Healthcare professionals should continue to provide nationally recommended childhood vaccinations to children on the autism spectrum, including the Measles, Mumps, Rubella (MMR) vaccine. [EM2-6]***

GPP 2.7 ***Routine heavy metal (i.e., antimony, aluminium, arsenic, cadmium, lead, manganese, mercury, nickel, silver, and thallium) concentration testing or screening is not recommended for children on the autism spectrum as there is insufficient evidence for any causative link. [EM2-7]***

GPP 2.8 ***Healthcare professionals may consider investigating for mercury toxicity in selected children on the autism spectrum who present with serious neurological and immunological problems. [EM2-7]***

GPP 2.9 ***Healthcare professionals may consider investigating for lead toxicity in selected children on the autism spectrum where pica is suspected or diagnosed. [EM2-7]***

2.4 INVESTIGATIONS IN CHILDREN AND ADOLESCENTS ON THE AUTISM SPECTRUM

The objectives of investigating children and adolescents diagnosed with autism are to detect an underlying aetiology, especially genetic or syndromic causes, screen for co-occurring conditions (if any), and counsel parents on the probability of recurrence in future pregnancies. The range of investigations (genetic testing, magnetic resonance imaging of the brain, electro-encephalography and metabolic testing) is wide and should be considered after balancing the potential yield against the cost-benefit to the individual child.

Following a diagnosis of autism, investigations into the cause for autism may be initiated after the professional obtains a thorough history, explores the family history (of at least 3 generations) and performs clinical examination. The healthcare provider must apply professional judgment to the specific clinical circumstances presented by the individual patient and balance the benefits of testing against the issues of diagnostic yield, cost and practicality. A positive result on genetic testing may allow some parents to resolve their suspicions regarding the cause for autism. An identified genetic aetiology of autism enables parents to seek relevant services, facilitates at-risk screening of other organ systems (e.g., brain, heart and kidneys in tuberous sclerosis) and allows genetic counselling on the recurrence risks in the next pregnancy.[161,162]

Genetic testing of children with a diagnosis of autism may be considered, and the approach of genetic testing is dependent on the clinical features, family history and parental wishes. In children with non-syndromic autism and absent family history of autism, genetic testing may be offered to identify for any *de novo*, likely gene-disrupting genetic variant(s) in genes that may contribute to autism. The phenotypic spectrum of features in autism is wide and known to be highly heritable. Variations in the genes may

be relatively large (traditionally detected through chromosomal microarray) or small (detected through whole exome sequencing). Such variations could be due to copy number variations (CNV; due to gene insertion, duplication, deletion), single nucleotide variants, or epigenetic alterations. These modifiers (or factors that modulate the expression of genes) can alter convergent signalling pathways and lead to impaired neural circuitry formation. Kreiman and Boles (2020) have published a practical guide containing state-of-the-art genetic testing for children on the autism spectrum.[163] Given the large number of genetic variants described, it is beyond the scope of this guideline to list all variants here, and the reader is advised to consult genetic specialists.

In 2013, the American College of Medical Genetics and Genomics (ACMG) provided guidelines for physicians on the clinical genetics evaluation in identifying the aetiology of autism.[161] It is important for parents and caregivers of children on the autism spectrum to be provided with *clinical correlation* of the features and genetic variation that is found following testing. This is part of post-test counselling and requires close collaboration between the physician and geneticist.

Ideally, genetic testing should be recommended for all children on the autism spectrum because a cause may be found in some 20 – 30% of cases depending on the test used and the underlying clinical presentation. However, given practical considerations of cost and feasibility, genetic testing should be offered to individuals with other clinical features and/or family history to suggest an underlying genetic cause. Genetic evaluation for individuals with isolated autism and/or absent family history may still be considered especially if parents are keen to understand the recurrence risk in a future pregnancy.

GPP 2.10 ***Children who present with autism and have additional clinical features suggestive of an underlying genetic condition (such as microcephaly, seizures, dysmorphic features, congenital anomalies or a positive family history of developmental disability) should be referred to a genetic specialist for diagnostic confirmation and counselling. Examples of genetic conditions or syndromes include Fragile X syndrome, Angelman syndrome, Tuberous Sclerosis, Rett syndrome, PTEN Hamartoma syndrome and Down Syndrome. [EM2-1]***

GPP 2.11 ***Children who are diagnosed with autism may benefit from genetic testing which can be offered by healthcare professionals. Discussion on the exact genetic test(s) to consider should be conducted by a genetic specialist or similarly-trained professional. [EM2-1]***

2.4.1 Types of Genetic Testing

Chromosomal microarray (CMA) is the first choice of genetic testing for the aetiology of autism in children. CMA utilises either array comparative genomic hybridization (aCGH) or single nucleotide polymorphism (SNP) techniques to scan the genome for CNV such as insertions, duplications or deletions of genes. In 2010, the American Society of Human Genetics (ASHG) issued a Consensus Statement regarding the utilisation of CMA for genetic testing of individuals with unexplained developmental delay/intellectual disability (DD/ID), autism or multiple congenital anomalies (MCA).[164] In the above conditions, CMA offers a much higher diagnostic yield (15%-20%) for genetic testing as compared to G-banded karyotype (3%). Evidence therefore strongly supports the use of CMA in place of G-banded karyotyping as the first-tier cytogenetic diagnostic test for patients with DD/ID, autism or MCA. G-banded karyotype analysis should be reserved for patients with obvious chromosomal syndromes (e.g., Down syndrome), a family history of chromosomal rearrangement, or a history of multiple miscarriages.

The diagnostic yield from genetic testing to evaluate aetiology of autism was reportedly 8% to 21% in the past, depending on the referral pattern and geneticist's clinical experience, but increased to over 20% when CMA was performed for children on the autism spectrum having the above additional features.[165,166]

Where there is a CNV (as an insertion, deletion or duplication) detected in a child, genetic counselling is recommended and parental blood samples may be required to establish if the CNV had arisen *de novo* or was inherited from a parent.

Fragile X testing is indicated to confirm the diagnosis in all boys presenting with unexplained autism with or without typical signs (frontal bossing, long jaw, large ears, large testes with delayed milestones). Most cases of fragile X cases are caused by expansion of a trinucleotide repeat within the *FMR1* gene on the X chromosome. Fragile X testing counts the number of repeat trinucleotides to determine if the number is consistent with disease or reproductive risk of disease.

About 20% of boys with fragile X syndrome meet the diagnostic criteria for autism.[122] Conversely, the diagnostic yield of fragile X testing was found to be nearly 5% in an unselected cohort of boys on the autism spectrum.[169] Although there is no evidence to support offering routine fragile X testing to girls, fragile X testing should be considered in females with autism with (i) a phenotype suggestive of fragile X; (ii) a family history suggestive for X-linked neurodevelopmental disorders; (iii) premature ovarian insufficiency, ataxia or tremors in close relatives.[161].

When the history and physical examination, CMA, and fragile X analysis do not identify an aetiology, targeted multi-gene panel, whole exome sequencing (WES) and/or whole genome sequencing (WGS) techniques can be considered as next steps to evaluate the aetiology of autism. In a population-based sample of 258 children on the autism spectrum referred from developmental paediatric clinics in Canada from 2008 through 2013, the molecular diagnostic yield of WES (8.4%) was comparable with the yield from CMA (9.3%). A combined molecular diagnostic yield of 15.8% was found in those children who received both tests.[167] In addition to WES or WGS, targeted multi-gene panels using next generation sequencing (NGS) is available for clinical evaluation of children on the autism spectrum.[168] These targeted gene panels, some containing as many as 2000 genes, are typically less costly, with high gene coverage, and can be considered as an alternative testing option before embarking on WES or WGS.

In recent years, there is increasing evidence that may support the use of WES and/or WGS as a first-tier genetic test for autism. A meta-analysis by Srivastava et al. (2019) proposed WES as a first-tier test due to a favourable diagnostic yield of 39% for neurodevelopmental disorders as a group (ID and/or autism), and 16% for autism. A similar proposal was made by Arteche-Lopez et al. (2021) as they reported that, compared to CMA and fragile X syndrome testing, there was a higher diagnostic yield using WES for patients on the autism spectrum (without clinical suspicion for fragile X syndrome).[859] An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG) for the use of WES and WGS was published in 2021 and recommended that WES and WGS be considered as first- or second-tier tests for paediatric patients with congenital anomalies or intellectual disability. Although isolated autism was out of the scope for the recommendation, the authors commented that the use of WES and WGS is expected to have similar clinical utility for evaluation of isolated autism.[860]

As the cost of WES and/or WGS continues to reduce over time with more established evidence showing cost-effectiveness in diagnosing autism, it is possible that WES and/or WGS will supersede CMA as first-tier testing in the near future.

Multi-gene panels, WES and WGS are advanced genetic testing techniques that should be carried out by accredited geneticists familiar with pre-test and post-test parental counselling, in accordance with the *Ministry of Health Code of Practice on the Standards for the Provision of Clinical Genetic/Genomic Testing Services and Clinical Laboratory Genetic/Genomic Testing Services (MOH CF 078:083 dated 28 June 2018).* Although WES can sequence practically all genes in an exome, most commercial WES tests do not include information on trinucleotide repeats (such as fragile X syndrome), or imprinting/methylation (such as Angelman syndrome).

- In summary, the diagnostic yields to be expected in a genetic evaluation of autism are as follows:[161,861]CMA (10%)
- Fragile X syndrome (1–5%)

- *MECP2* (Rett syndrome; 4% of females)
- *PTEN* (PTEN Hamartoma syndrome; 5% of those with head circumferences >2.5 SDs that are tested)
- Karyotype (3%)
- WES/WGS (36% overall for isolated neurodevelopmental disorders including autism).

2.4.2 Other Investigations

Magnetic resonance imaging (MRI) of the brain may be indicated in *selected* children on the autism spectrum who present with signs of microcephaly, regression of developmental milestones or where structural brain lesions are suspected clinically. This should only be conducted following discussion with a specialist physician. However, MRI of the brain should *not* be routinely performed in all children on the autism spectrum,[170] because of the lack of a single pathology associated with autism and the risk of sedation required to perform imaging.

GPP 2.12 ***Magnetic resonance imaging (MRI) of the brain may be performed in selected children on the autism spectrum who present with microcephaly, milestone regression or where structural brain lesions are suspected. [EM2-8]***

A systematic review was conducted by Gurau et al. (2017) to examine evidence for the utility of 3 methods of electroencephalography (EEG) signal analysis in autism diagnosis and subtype delineation, by classifying them according to the principal methods of EEG analyses: functional connectivity analysis, spectral power analysis and information dynamics.[171] All 40 studies in the systematic review identified significant differences between individuals with and without autism. However, due to high heterogeneity in the results, generalisations could not be made and none of the methods alone are currently useful as a new diagnostic tool. These results confirm the presence of EEG abnormalities in autism,[171] but these are insufficient to help in the diagnosis. EEG should only be conducted following discussion with a specialist physician.

GPP 2.13 ***Electroencephalography (EEG) may be performed in selected children on the autism spectrum who develop clinical seizures, seizure-like movements and/or regression of developmental milestones. [EM2-8]***

Several inborn errors of metabolism (IEM) are known to be associated with autism, and there is a higher prevalence of IEM in autistic individuals in countries with high rates of consanguinity. Furthermore, some IEM are treatable with immediate improvement in symptoms when the treatments are started early in life. On the other hand, large cohort studies have observed that metabolic disorders associated with an autism phenotype are relatively rare. Hence the American College of Medical Genetics and Genomics and the American Academy of Paediatrics do not recommend routine metabolic screening in all children on the autism spectrum, unless there are additional indications. These indications include cyclic vomiting, microcephaly, dysmorphic features, ataxia, epilepsy and ID. Metabolic screening is also recommended for children who are born into families with a high degree of consanguinity, or who have not had newborn metabolic screening.

In a large multi-centre Spanish study reported by Campistol et al. (2016), 406 patients (mean age 6.71 years, SD 4.15) with non-syndromic autism underwent urine analysis to assess the diagnostic yield of IEM, after excluding individuals with neurologic symptoms, dysmorphic features, renal and cardiac anomalies.[172] Campistol et al. found only one patient with a urea cycle disorder and concluded that metabolic screening is not cost-effective and should not be considered for non-syndromic autism in children without neurological signs.[172]

A similar conclusion was made by Schiff et al. (2011) who analysed the results of a metabolic workup (urinary mucopolysaccharides, urinary purines and pyrimidines, urinary creatine and guanidinoacetate, urinary organic acids, plasma and urinary amino acids) that was routinely performed in 274 non-syndromic autistic children in France.[173] Only 2 of 274 children were found to have abnormal result (non-specific creatine urinary excretion, persistent 3-methylglutaconic aciduria), suggesting that routine

metabolic screening did not contribute to the aetiology of non-syndromic autism.[173] The prevalence of screened IEM in non-syndromic autism was probably not higher than in the general population (<0.5%).

Metabolic investigations may be indicated in selected children on the autism spectrum but is not recommended as a routine investigation for all. Children with clinical features such as regression, failure to thrive, family history of death in early childhood, associated hearing or visual impairment, and dysmorphic features may have a concurrent metabolic condition that warrants further investigation. Such children should be evaluated by a trained genetic specialist to guide investigations. These may include plasma acylcarnitine levels, urine organic acids levels and plasma amino acid levels as well as other specific tests guided by the clinical history. Routinely performing these tests for all children on the autism spectrum is not recommended due to a very low yield.[172,173]

GPP 2.14 ***Targeted screening for an inborn error of metabolism (IEM) may be indicated in selected children on the autism spectrum who present with clinical features such as cyclic vomiting, microcephaly, ataxia, epilepsy, intellectual disability or have a family history of consanguinity. [EM2-8]***

Given the lack of conclusive evidence supporting any association between heavy metal exposure, such as mercury, magnesium and zinc with autism, there is no evidence to recommend routine testing for these metals in any medium (blood, hair, urine or stool) in children and adolescents on the autism spectrum.[159,174] Within our local Singaporean context where environmental lead exposure is low, routine testing for blood lead levels is not recommended for all autistic children, unless there are specific factors in the clinical history that suggest a risk for lead exposure.[175]

See earlier GPPs 2.7 to 2.9.

There is currently insufficient evidence to support the testing of stool for microbiota profile in children on the autism spectrum. Although there is growing evidence for possibly altered gut microbiome profile in individuals on the autism spectrum, with potential treatment implications, this is inconclusive and has not translated into meaningful clinical treatments and outcomes.[176–178] For those children who have specific gastrointestinal symptoms, such as abdominal pain or diarrhoea, investigations should be carried out as indicated, similar to all children with similar symptoms.[179]

GPP 2.15 ***Routine stool investigations to test for yeast or microbiota profile are not recommended for children on the autism spectrum. [EM2-8]***

Abbreviations

aCGH, array comparative genomic hybridization; ACMG, American College of Medical Genetics and Genomics; ASHG, American Society of Human Genetics; CMA, chromosomal microarray; CNV, copy number variations; DD/ID, developmental delay/intellectual disability; EEG, electroencephalography; IEM, inborn errors of metabolism. MCA, multiple congenital anomalies; MMR, Measles, Mumps, Rubella; MRI, magnetic resonance imaging; NGS, next generation sequencing; SNP, single nucleotide polymorphism; WES, whole exome sequencing; WGS, whole genome sequencing.

CHAPTER 3: INTERVENTION

A wide range of interventions have been designed, developed or adapted for individuals on the autism spectrum. The modalities that are included as interventions are largely mainstream approaches, defined as evidence-based standard care practices that have demonstrated efficacy in the larger population. These may include practical strategies targeting specific outcomes such as speech and communication skills, therapeutic programmes with strong theoretical foundations, and approaches with a clear mechanism of change on outcomes that are central to the core symptoms of autism. Novel or non-mainstream approaches that may or may not improve outcomes in the general functioning of individuals (with or without autism) are considered under complementary or alternative approaches.

The objectives of intervention are to promote child health and well-being, enhance emerging competencies, minimise developmental delay, remediate disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning. These goals are accomplished by providing individualised developmental, educational and behavioural intervention services for children in conjunction with mutually planned support for their families.[180–184] There is a wide range of activities that constitute intervention. These can range from child-targeted activities or child's involvement in structured centre-based activities, to parent-mediated intervention and outcomes-based therapies. Intervention may be individualised and a combination of interventions that utilise various elements of different methods may be employed for a particular child. The efficacy and safety of any intervention should be validated through well-designed research.

Intervention is best planned and conducted in a collaborative manner between professionals and a child's parents and caregivers. Often, it would be useful to involve the child in the process of decision-making and planning of goals for intervention. Skills can be developed and practised in a range of settings, for example, centre-based programmes, home-based programmes or parent-mediated intervention.

Intervention may be provided by different professionals who have relevant and adequate training and clinical expertise. Continual communication and partnership among professionals supporting the child with autism is fundamental. For example, psychologists, teachers and therapists together with parents and caregivers, may play different roles in the promotion of social communication skills in a child on the autism spectrum. While psychologists and therapists may provide formal assessments and design intervention targets, these may be done holistically with valuable insights and input from teachers and parents or caregivers. What has been taught during the formal intervention sessions would also need to be practised and generalised in the everyday environment beyond the clinical settings. It is crucial to formulate an individualised plan with input from a variety of specialists, in response to the changing needs of the child on the autism spectrum across the developmental phases. Monitoring of response to any intervention is also a core element and responsibility in all clinical practice.

The following intervention modalities reviewed in this chapter are ordered alphabetically, many of which refer to the type of intervention approach and not a specific programme. They are child-focused, independent of the implementation settings, and may target a range of outcomes associated with the core symptoms of autism. Parent- or caregiver-mediated approaches are considered separately (See **Chapter 9: Caregiver and Family Support**) as these are non-standardised methods and usually involve the training and acquisition of skills and competency of non-medical professionals in supporting the child who is on the autism spectrum.

3.1 AUGMENTATIVE AND ALTERNATIVE COMMUNICATION (AAC)

Augmentative and Alternative Communication (AAC) refers to all of the ways that someone communicates besides talking. People of all ages can use AAC if they have trouble with speech or language skills. Augmentative means to add to someone's speech. Alternative means to be used instead of speech. Some people use AAC throughout their life. Others may use AAC only for a short time, like when they have surgery and can't talk. There are a lot of different types of AAC. No-tech and

low-tech options include things like gestures and facial expressions, writing, drawing, spelling words by pointing to letters, and pointing to photos, pictures, or written words. High-tech options include things like using an app on an iPad or tablet to communicate and using a computer with a “voice," sometimes called a speech-generating device.[185] These can be found at Assistive Technology - Disability Support | Enabling Guide. There is emerging evidence to suggest that for children and adolescents on the autism spectrum, the use of AAC can lead to improvements in communication, and in some cases, improvements in behaviour, joint attention, and play skills.[186] Although there is insufficient research on the efficacy of AAC to improve speech-related outcomes, research has shown that AAC does not hinder speech. Further rigorous research is warranted in the area of AAC.

R 3.1 ***Augmentative and Alternative Communication (AAC) may be used for children and adolescents on the autism spectrum to support communicative understanding and expression. The AAC system should be customized to the individual's communication needs, preferences and environment. [EM3-1]***

3.2 COGNITIVE BEHAVIOURAL THERAPY (CBT)

Cognitive behavioural therapy (CBT) is a type of psychological treatment that has been extensively studied and proven to be effective in treating a range of problems including depression and anxiety disorders, eating disorders, and other severe mental health conditions. CBT has consistently been reported to lead to significant improvement in functioning, remediation of symptoms and enhanced quality of life, when compared to other forms of therapeutic approaches or psychiatric medications. Modern CBT is based on the following core principles: problems are a result of unhelpful or faulty ways of thinking, problems are based on patterns of unhelpful or maladaptive behaviour, and individuals can be relieved of their psychological problems by learning better ways of coping.[187] There are many techniques involved in CBT, ranging from psycho-education about the presenting problem, the use of ‘homework’ exercises, emotional literacy and regulation skills, and Socratic questioning to exposure exercises. Advances in CBT have been made based on research evidence and clinical practices.

CBT has also been extensively applied and validated in treating a range of conditions in children and adolescents, especially emotional-related issues such as anxiety. When applying CBT to children and adolescents on the autism spectrum, modifications and adaptations are recommended. There is an increasing number of studies examining the efficacy of CBT programmes in the autistic population. Current evidence suggests low to moderate effects and certainty of evidence of CBT interventions in treating emotion-based conditions such as anxiety in autism.[188–193] While there are positive effects of CBT treatment on other important outcomes such as hyperactivity, challenging behaviours, sleep,[194–196] further research will be required to support the evidence. Some positive effects of CBT treatment were reported on social communication and sensory behaviours, cognition, adaptive behaviour, and learning in individuals on the autism spectrum, but the quality of evidence was determined to be moderate to low.[23,24,197,198] In so far, the efficacy of CBT has been applied to specific profiles of autism, e.g., verbal and cognitive-intact individuals.

R 3.2 ***Cognitive Behavioural Therapy (CBT) may be used for children and adolescents on the autism spectrum who have sufficient verbal and reasoning abilities, to address emotion-related issues such as anxiety and anger. Modifications may be required to facilitate understanding and application of CBT strategies in this population. Involvement of caregivers can support the generalization of strategies for younger children. [EM3-2]***

3.3 COMMUNICATION-BASED INTERVENTIONS

3.3.1 Pivotal Response Training (PRT)

Pivotal response treatment (PRT) is a comprehensive child-initiated intervention approach, derived from applied behaviour analysis.[199] It spans both Communication-based and Naturalistic Developmental

Behavioural Intervention approaches. The child's motivation is central in PRT to promote learning of communication skills and positive social behaviours that are functional and embedded in the child's natural environment. Teaching methods include using child choice, task variation, and natural direct consequences. PRT intervention is tailored for the individual child's goals, needs, and routines, involving implementation by family members and others in the child's life, to effect widespread improvements in communication, behaviours, and social skills. Research from randomised clinical trials (RCTs) have reported significant and large improvements in expressive language and social initiation, but inconsistent positive or null findings for receptive language skills.[200–202] No adverse effects or risks of harm were reported. Pacia et al. (2022) found that parent-mediated PRT qualified as an established evidence-based practice for social communication targets, and may be recommended to improve language and social communication outcomes.[202] However, the certainty of evidence was reduced due to concerns of inconsistency and imprecision affecting results in studies, and more high-quality research is needed to ascertain its effectiveness.

3.3.2 Language Training

Language training includes practices that support language production such as modelling, prompting, differential reinforcement, and visual supports. Language training did not emerge as a focused intervention in systematic reviews.[23] It is proposed that language training supports be delivered by the people (e.g., parents, professionals) who are likely to lead to the most meaningful and sustained increase in the child's learning, participation, and wellbeing.[10] Supports involving professionals and caregivers resulted in greater therapeutic effects on expressive language (spoken language) than supports from professionals or caregivers alone.[203] However, research on communication skills outcomes have reported mixed positive or null effects following language training. Language training practices may be recommended to support development of expressive language in children on the autism spectrum. Implementation should involve professionals and caregivers to facilitate language gains and increase therapeutic effects.

3.3.3 Speech Intervention

Children on the autism spectrum who are verbal may display abnormal speech prosody impacting on their social interactions. Interventions generally involve using established evidence-based practices (such as video-modelling, antecedent-based intervention, prompting/instruction, scripting and reinforcement) to target abnormal prosody in global intonation, affective intonation, contrastive stress, pitch, speech rate and intensity. One systematic review of studies involving single-case and group designs reported moderate to large improvements in autistic persons who have abnormal prosody, with largest effect sizes in intensity and global intonation in prescribed contexts. Research representation is uneven with greater focus on verbal children and adolescents on the autism spectrum. However, studies were mostly low in quality, making it difficult to draw firm conclusions on efficacy.[204] There is limited evidence for speech interventions at present. It is generally suggested that using established techniques to target prosody is more likely to result in improvements than other techniques for autistic individuals whose prosodic patterns may pose a barrier to communication.

3.3.4 Functional Communication Training (FCT)

Functional Communication Training (FCT) is a set of practices that replaces a challenging behaviour that has a communication function with more appropriate and effective communication behaviours or skills. A functional behaviour assessment is conducted to identify the function of an interfering or problem behaviour, followed by teaching an appropriate communication skill that may serve the same purpose for the autistic individual. FCT often includes a differential reinforcement procedure in which an individual is taught an alternative response that results in the same class of reinforcement identified as maintaining problem behaviour. Problem behaviour is typically placed on extinction. The distinct component of FCT is that the alternative response is a recognisable form of communication, e.g., a vocalization, manual sign, Picture Exchange Communication System®.[23] For social communication and communication outcomes, two systematic reviews reported positive effects of FCT but the quality of

both reviews was low.[24] No evidence was reported for receptive language and expressive language outcomes. FCT was identified as an emerging intervention (some positive evidence but not enough to qualify as evidence-based) by the National Standards Project.[24]

R 3.3 ***Communication-based interventions (e.g., language training, pivotal response training) may be used for children and adolescents on the autism spectrum as they lead to improved social communication outcomes (including joint attention, social engagement and initiation), and may lead to improved receptive language, expressive language, and speech prosody outcomes. [EM3-3]***

3.4 DEVELOPMENTAL INTERVENTIONS

Developmental interventions refer to a group of intervention practices based on the constructivist theory of learning, which focuses on improving the child-adult synchrony, reciprocity and parent-child interaction so as to ameliorate the difficulties in social interactions and related skill differences in the child. The intervention is generally child-led and implemented according to developmental sequence. Examples of developmental intervention practices include Developmental Individual-Difference Relationship-Based/Floortime (DIR/Floortime); Hanen More than Words, and Paediatric Autism Communication Therapy.

The review of existing literature indicated a moderate size of good quality evidence evaluating the efficacy of developmental interventions.[205] The findings of available meta-analyses and systematic reviews of the assortment of developmental interventions show relatively consistent results with respect to the magnitude and areas of improvement seen as a result of developmental interventions for children on the autism spectrum. Developmental interventions as a group have moderate to large effects on improving social interaction and social communication for children on the autism spectrum. One meta-analysis reported small effects on general outcomes.[206] No effect was found on communication and motor skills. The confidence in the quality of available evidence on the effect of developmental interventions may be potentially threatened by high risk of attrition bias and relatively few studies evaluating distal and generalised outcomes.

In addition, a large proportion of current literature on developmental interventions consists of studies investigating effects of several prominent trademarked developmental interventions (e.g., DIR/Floortime) on children on the autism spectrum. The findings of developmental interventions are likely over-shadowed by effects of those specific intervention practices. Further high-quality studies are needed to evaluate the effects of other developmental intervention practices.

R 3.4 ***Developmental interventions, (a group of interventions that are implemented based on developmental sequence and focus on supporting children's learning of skills through interactions with other people, particularly caregivers) may be used for children and adolescents on the autism spectrum to improve core difficulties in social communication and social interactions. [EM3-4]***

3.5 EARLY INTENSIVE BEHAVIOURAL INTERVENTION (EIBI)

Early Intensive Behavioural Intervention (EIBI) represents a class of interventions where procedures, based on the principles of behaviour analysis, are employed to help a person acquire new skills or reduce the occurrence of specific behaviours. These approaches usually include components such as activity embedded trials, differential reinforcement, discrete trial training, incidental instruction, and prompting, etc. It is one of the most thoroughly researched early intervention approaches for children on the autism spectrum.

Research suggests that EIBI is a helpful intervention approach for supporting the development of children on the autism spectrum.[207,208] There is low to moderate evidence suggesting that when implemented by trained professionals and with intensity, children can make gains, usually with small to medium effect sizes, in multiple areas of development. However, research also indicates that EIBI does

not have an effect of improving the overall symptoms of autism. It is generally proposed that intervention needs to be intense and regular, but there is currently limited evidence for its optimal intensity and for who will respond positively to EIBI. It should also be noted that some members of the autism community have questioned the ethics of EIBI, given that early versions of EIBI may have had some components with aversive treatment procedures.[862] However, EIBI continues to evolve and such treatment procedures are now minimised in most instances.

R 3.5 ***Early Intensive Behavioural Intervention (EIBI) may be considered to improve the development of adaptive skills and cognitive ability in children on the autism spectrum. It should be implemented by trained professionals and with sufficient intensity and be based on the intended goals for the child and family. [EM3-5]***

3.6 EMOTIONAL REGULATION THERAPY (ERT)

Emotional Regulation Therapy (ERT) involves a range of treatment modalities designed to teach emotion recognition, perception, regulation and management skills. It encompasses a range of social pragmatic methods and materials such as computer-based software programmes or applications, videos and games. Examples of such programmes include the Social Communication, Emotion Regulation, Transactional Support (SCERTS) program, Let's Face It! Program, and technology-based interventions such as the Transporters DVD.

There is emerging and promising evidence that some form of ERT can have a positive outcome on core symptoms of autism such as social communication skills.[209,210] Null pooled effects were reported on outcomes related to overall autism characteristics, cognition, play skills, challenging behaviours and adaptive behaviours.[211,212] Overall effect and quality of studies are currently low. The effectiveness of the ERT and associated targeted outcomes is dependent on the modality of ERT adopted, as well as the delivery method of the program. There is a lack of standardised procedures in the adoption of ERT although the programmes are based on emotion learning theories.[213] These limit the quality of scientific evidence. The generalisability of the reported improvements to real-life social contexts are further compromised by limited sample size and inconsistencies in methodologies.[214] More studies evaluating the effectiveness of each of these programmes will be required.

R 3.6 ***Emotion Regulation Therapy (ERT) involves a range of treatment modalities (e.g., computer software programmes, videos, games) to teach emotion recognition, perception, and management skills, in children and adolescents on the autism spectrum, using a social pragmatic approach. ERT-based intervention may be considered for improving emotion recognition and socio-communication skills in children and adolescents on the autism spectrum. [EM3-6]***

3.7 NATURALISTIC DEVELOPMENTAL BEHAVIOURAL INTERVENTIONS (NDBIS)

The intervention category of Naturalistic Developmental Behavioural Interventions (NDBIs) refers to a group of intervention practices that integrates behaviour and developmental theories. NDBIs are based on behavioural principles but applied in a way that emphasises their delivery in the context of developmentally appropriate adult-child interactions, with a focus on learning in the context of play and routine activities and using natural contingencies to shape behaviours.[215] Some characteristics of NDBIs include: 1) Skills are taught in developmental sequence; 2) Intervention targets skills across developmental domains; 3) Intervention often aims to prompt social engagement and interaction; 4) Behaviour principles are used to shape new skills.

As indicated in the Autism CRC report (2022), the commonly studied NDBIs include caregiver-based intervention programmes in community day-care centres; Denver Model; Early Social Interaction Project (ESI); SCERTS;[216] Early Start Denver Model (ESDM);[217,218] Focus parent training program; Home-based Building Blocks Program; ImPACT Online; Interpersonal Synchrony; Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER);[219] Joint Engagement Intervention with

Creative Movement Therapy; Joint Engagement Intervention; Learning Experiences Alternative Program (LEAP); Parent-Early Start Denver Model (P-ESDM); PRT; Reciprocal Imitation Training (RIT);[220] and Social ABCs.[221]

There is a large body of studies evaluating the efficacy of NDBIs. However, due to the variability among the intervention practices and outcome measures, a large proportion of current literature consists of studies that have investigated the quantifiable outcomes of specific NDBIs on children on the autism spectrum. Few have evaluated the effects of the NDBIs as a group. The findings of available meta-analyses and systematic reviews of the assortment of NDBIs show relatively consistent results with respect to the magnitude and areas of improvements as a result of NDBIs for preschool children on the autism spectrum.[206] NDBIs as a group have moderate to large effects on reducing social communication difficulties, improving language, cognitive and play skills. However, the confidence of the quality of available evidence on the effect of NDBIs may be potentially threatened by high risk of detection bias and relatively small effect on distal and generalised outcomes. In addition, there are still concerns about the context-boundness and proximity of outcomes measured in the studies.

Several studies assessed the relationship between the amount of intervention and the intervention effect, and the findings support the efficacy of low-intensity NDBIs. Tiede and Walton (2019) found that the intervention dosage only affects intervention effect on joint attention, but not on outcomes on social communication, language, cognition, play, and adaptive behaviours.[222] The review by Crank et al. (2021) also indicated that the intervention effects of NDBIs did not differ significantly by factors such as the participant or intervention characteristics, intervention intensity, and type of the interventionist who delivered the intervention.[223]

R 3.7 ***Naturalistic Developmental Behavioural Interventions (NDBIs) (a group of intervention practices that integrate behavioural and developmental theories, which are delivered in natural settings and use child-centred and motivation-based strategies to teach developmentally appropriate skills in the context of play and routine activities) may be used for children on the autism spectrum to improve social communication, language, cognitive, and play skills. [EM3-7]***

3.8 PLAY-BASED INTERVENTION

Play is often considered as a naturalistic and engaging context to teach children and adolescents on the autism spectrum critical social skills. Play-based intervention may include generic play involving a variety of materials such as games, toys and activities, or structured programmes, commonly targeting play and social communication skills. Play-based intervention can have benefits in providing opportunities of learning and appropriate engagement for children on the autism spectrum although they may not have a direct impact on the core symptoms of autism. Play-based interventions focus on supporting children's learning through interactions with others. These interventions target skills that are either delayed or not apparent in children on the autism spectrum, but are assumed to be critical to learning. These skills include initiating interactions and sharing interest (e.g., use of gestures, joint attention), observing and then copying others' behaviour (e.g., imitation), and taking turns in play sequences as well as early conversations.[211] Developmental interventions are often described as being 'child-led', because they use children's intrinsic motivation to communicate; and 'naturalistic', because of the contexts in which they are delivered. There is minimal risk of harm for play-based interventions, which are naturalistic and part of the developmental process of children, providing ideal opportunities and contexts for parent and peer engagement. Play therapy, on the other hand, is a non-directive approach to incorporate play activities to address emotional and behavioural issues in children. There is a lack of studies examining the efficacy of play therapy in children and adolescents on the autism spectrum.

While some studies examining play-based intervention in children on the autism spectrum reported encouraging results such as improvements in specific social and communication skills and play skills, the findings are limited in generalizability and replicability. One meta-analysis studied the efficacy of

play-based interventions to address play skills of children on the autism spectrum (aged 2-12).[224] Nineteen studies which comprised generic play intervention, JASPER, Lego therapy, Social Stories, behavioural approaches, peer training, teacher training, SENSE Theatre principles, video modelling were included. The studies comprised 11 pre-post within-group analyses of intervention groups, and eight between-group analyses. Results indicated a positive pooled effect but the intervention format and setting did not relate to effects on play. Interventions that focused on the child were associated with improved play skills in the child compared to interventions that focused on parents, peers, or teachers. There were no reported direct effects on core symptoms of autism. More rigorous studies are required to establish the consistency in the evidence, especially in terms of modality of treatment, dosage regime, and mode of delivery. Longer term studies are required to examine the sustainability of the effects.

R 3.8 ***Play-based intervention may involve the use of a variety of materials such as games, toys and activities to address play and social communication skills, while play-therapy is a non-directive approach that aims to address emotional and behavioural issues. These approaches may be used with children on the autism spectrum to improve language, joint-attention and social engagement skills, especially for those aged 12 years and below. [EM3-8]***

3.9 SENSORY INTERVENTIONS

3.9.1 Sensory Integration Therapy

Sensory integration therapy involving elements as described by Ayres is based on principles of neuroscience and includes both theoretical framework and practice guidelines designed to address sensory processing difficulties and to support learning and social participation in children.[225,226] It uses child-directed activities to challenge the child to actively participate in sensory activities and produce adaptive responses. Sensory integration therapy is provided within a professional context, often in a sensory-motor gym that provides enriched tactile, proprioceptive and vestibular inputs. Caregivers are important collaborators and are often involved in the goal setting, treatment planning and evaluation process.

Evidence from 5 RCTs and 1 quasi-experimental study indicate that there is moderate to high certainty of evidence that there is improvement in functional and social participation outcomes, with effect size ranging from moderate to high, after sensory integration therapy.[227–232]

R 3.9 ***Sensory integration therapy involving elements as described by Ayres may be recommended as a therapeutic intervention in children (3-12 years old) on the autism spectrum to improve functional and social participation outcomes. [EM3-9]***

3.9.2 Sensory Environmental Modification and Sensory Modulation Strategies

It is estimated that the majority of children and adolescents on the autism spectrum experience aversion to sensory inputs or excessively seek out sensory stimuli (See **Chapter 7: Co-occurring Conditions**). Children with specific sensory needs may benefit from sensory environmental modification and the use of sensory modulation strategies. Examples include adapting the dental environment to reduce behavioural aversiveness during dental cleaning, and the use of movement breaks to reduce fidgety and sensory-seeking behaviour in the classroom.

More evidence on sensory environmental modification and use of sensory modulation strategies has become available over the past 10 years, including systematic reviews and RCTs.[233–235] Overall, the use of such interventions showed some benefit with reduction in aversive behaviours and improvement in ability to self-regulate.[233–235] However, these findings were limited by heterogeneity of population groups and intervention used, differences in outcome scales used, small sample sizes and lack of long-term data, thus limiting the confidence in reported effects.[233–235] Of note, many of the limitations contributing to low confidence in the reported effects are inherent to the intervention delivered and

population studied. Hence, it should not be expected that more studies would improve the generalisability of findings.

Nevertheless, the potential for harm in the use of environmental modification and self-regulation strategies is low. Positive and statistically significant trends across some of the outcomes suggest that these strategies can be considered for use in selected children and adolescents on the autism spectrum to address their specific sensory needs. Family education, monitoring, and overall informed consent on expected benefits should be discussed.

R 3.10 ***Sensory environmental modifications and sensory modulation strategies may be considered for selected children and adolescents on the autism spectrum to address their specific sensory needs. [EM3-10]***

3.9.3 Weighted Vests

The wearing of a weighted vest, or straps with evenly distributed weights, was postulated to reduce a range of problems in individuals on the autism spectrum, especially inattention and stereotypical behaviours. The weight prescribed and duration of use vary widely. Evidence on efficacy of weighted vests on reducing core autism symptoms is limited. There is insufficient evidence to support the use of weighted vests in children on the autism spectrum, with no RCT or quasi-experimental study found in the last 10 years.[233,236] In addition, there is a possible risk of harm as wearing weights beyond the prescribed weight limit and length of time may potentially affect musculoskeletal development.

R 3.11 ***Weighted vests are not recommended for use as a therapeutic intervention in children and adolescents on the autism spectrum due to insufficient evidence for benefit, and potential for harm. [EM3-11]***

3.10 SOCIAL SKILLS INTERVENTION

Social interaction difficulties are a core symptom in autism, appear early, continue to manifest as the child grows, and may be evident across different settings.[23,24] They are often the result of a lack of social awareness and limitation in social skills. A variety of social skills interventions has been developed to target different social skill areas. These may be implemented through a variety of formats including peer-mediated, caregiver-mediated, and professional-mediated programmes. They can also vary in purpose, duration, intensity and contexts. Social skills may be directly and explicitly taught to an autistic child through modelling and feedback or reinforcement.[180–183,237] Modelling is practiced when an adult or peer demonstrates the skill in real life or through video.[238–240] Feedback or reinforcement requires that the child with autism is taught a specific behaviour (such as regulating voice volume) and given positive feedback (or other forms of reinforcement) when the behaviour is elicited in the appropriate situation.

Current evidence suggests that social skills group intervention has a positive effect on child outcomes including anxiety, social communication skills, communication skills, cognition skills, challenging behaviours, play, adaptive behaviours, school and learning.[240–246] There is however insufficient evidence identifying specific social skills programmes to be more effective than others. Choice of specific intervention approaches should consider the child's developmental level, individual needs, preferences and environment.

R 3.12 ***Social skills intervention is recommended for children and adolescents on the autism spectrum to improve social communication and interaction skills. It can also lead to positive effects on challenging behaviours, adaptive and cognitive skills, and school and learning skills. The social skills intervention should be customized to the individual's needs, preferences and environment. [EM3-12]***

3.11 VISUAL SUPPORTS

Visual supports refer to a group of strategies that uses visual and concrete cues to inform on an activity or routine, provide clear expectations for behaviour, and teach or prompt children on the autism spectrum to perform target skills and behaviours. Visual supports are considered a focused intervention practice and can be a component of comprehensive intervention programmes.

A comprehensive intervention programme that incorporates the use of visual supports extensively is the Treatment and Education of Autistic and related Communication-handicapped CHildren (TEACCH). TEACCH is a comprehensive intervention model for children with autism and other developmental difficulties that uses environmental modifications to teach skills and reduce behaviour problems. Parents are engaged as co-therapists, and there is emphasis on developing life skills, enabling generalisation of the skills to different settings, and building independence for the child. The teaching approach of TEACCH is termed structured teaching, and the four main aspects of the approach are (1) physical organization: arrangement of the physical setting that the child is to perform or learn a skill in, (2) visual schedules: which inform the child of what activities and when the activities are to take place, (3) individual work systems: which inform the child on what needs to be done within an activity, and how to know when the activity is finished, and (4) visual teaching methods: which uses visual cues within a task to guide the child to complete the activity with as little teaching or prompting as possible. Structured teaching caters to the strengths and thinking styles of individuals on the autism spectrum, and can be used concurrently with other behaviour strategies. TEACCH is widely used in Singapore, although often in an eclectic approach in combination with other autism-specific intervention practices.

Evidence on the effectiveness of visual supports for children on the autism spectrum has increased over the past decade, with several systematic reviews, meta-analyses, and RCTs published. Overall, visual supports appear to provide improvements in some of the outcomes studied – such as academic outcomes, reducing challenging behaviours, cognitive or motor performance, and can capitalise on the stronger visual and spatial skills of autistic children. The use of visual supports is also recommended by other guidelines (e.g., Autism CRC, NICE, SIGN, NCAEP). There is sufficient evidence that the use of visual supports is beneficial for supporting children and adolescents on the autism spectrum.

R 3.13 ***Visual supports (e.g., pictures, objects, written words, lists, schedules, choice boards) should be used for children and adolescents on the autism spectrum. [EM3-13]***

3.12 INTERVENTIONS FOR SPECIFIC NEEDS

Children and adolescents on the autism spectrum can present with varying needs, and require varying levels of support across the developmental lifespan. While some approaches are more established than others, there are no studies to support the superiority of one intervention model over another.[10,16,23,247] The needs of the child, family preferences and availability of resources should be discussed when any specific intervention model or combination of approaches are considered. It is also important that the areas of needs are continually evaluated and addressed over time (See **Chapter 7: Co-occurring Conditions**).

Abbreviations

AAC, augmentative and alternative communication; ABA, applied behavioural analysis; CBT, cognitive behavioural therapy; DIR/Floortime, Developmental Individual-Difference Relationship-Based /Floortime; EIBI, early intensive behavioural intervention; ERT, emotional regulation therapy; ESDM, Early Start Denver Model; ESI, early social interaction; FCT, functional communication training; JASPER, Joint Attention, Symbolic Play, Engagement, and Regulation; LEAP, Learning Experiences Alternative Program; NDBIs, Naturalistic Developmental Behavioural Interventions; P-ESDM, Parent-Early Start Denver Model; PRT, pivotal response treatment; RCT, randomised controlled trial; RIT, Reciprocal Imitation Training; SCERTS, Social Communication, Emotion Regulation, Transactional Support; TEACCH, Treatment and Education of Autistic and related Communication-handicapped Children.

CHAPTER 4: PHARMACOLOGICAL TREATMENT

In children and adolescents on the autism spectrum, the management of behaviour, attention, mental health, and other issues (such as sleep) should be multi-modal and addressed in a multi-disciplinary setting. Examples of impairing behavioural or psychiatric symptoms in autism include hyperactivity, inattention, aggression, self-injury, anxiety, depression, tics, obsessive-compulsive behaviours, and sleep difficulties. While pharmacological agents may help to reduce such symptoms, psychological, behavioural, and environmental strategies should continue to be used in conjunction with pharmacotherapy. Consideration must also be given to each child's developmental differences, as well as any underlying medical disorders or significant social or environmental issues that might affect behaviour, attention, mental health and sleep. Pharmacological treatment of any co-occurring conditions in children and adolescents on the autism spectrum should only be undertaken by physicians with appropriate specialist training in the use of such medication. Physicians who prescribe more than one medication should be vigilant about the possibility of drug interactions, and monitor for clinical response and possible side effects. Response to medications may also be different for children and adolescents on the autism spectrum.

Although autism cannot be cured with medication, studies have evaluated the use of various pharmacological agents to improve the core symptoms of autism. This chapter therefore contains information on these as well.

Most available evidence on the efficacy of pharmacological treatment for children on the autism spectrum was for children over 5 years old and adolescents. Caution is therefore advised in extrapolating any of this evidence to preschool children. The use of pharmacotherapy in preschool children is generally discouraged. Table 4.1 summarises the recommendations arising from this chapter for easier reference.

Table 4.1: Summary of recommendations

Clinical Feature	**Summary of Recommendations**
Core symptoms of autism (social difficulties and RRBs)	No pharmacological agent has sufficient evidence to justify use. Ongoing research results are awaited for oxytocin and bumetanide.
Co-occurring conditions	*Attention-deficit Hyperactivity Disorder (ADHD)* • Methylphenidate should be the first line medication, and be used in conjunction with non-pharmacological approaches. • Atomoxetine may be considered if methylphenidate has been tried unsuccessfully or is contraindicated/not tolerated. • Guanfacine may be considered after methylphenidate and atomoxetine have been tried unsuccessfully or if they are contraindicated. *Challenging Behaviours and Psychiatric Conditions* • Risperidone and aripiprazole can be used for challenging behaviours (irritability and hyperactivity) in the short term. • In consultation with an appropriately trained specialist: ▪ SSRIs may be used to treat psychiatric conditions (e.g., anxiety, depression, OCD). ▪ TCAs may be considered as a second- or third-line option to treat psychiatric conditions (e.g., depression). ▪ Anticonvulsants/mood stabilisers may be considered as a second- or third-line option to treat challenging behaviours or psychiatric conditions. ▪ Mirtazapine may be considered as a second- or third-line option to treat anxiety.

	Sleep Difficulties • Melatonin can be considered for sleep issues if there is no benefit from a psychosocial intervention.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; RRB, repetitive restricted behaviour; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

4.1 PHARMACOLOGICAL AGENTS TARGETING CO-OCCURRING CONDITIONS IN AUTISM

4.1.1 Attention-deficit Hyperactivity Disorder (ADHD)

4.1.1.1 Methylphenidate

Methylphenidate is a stimulant medication that is widely used to treat ADHD, likely acting through catecholamines in the prefrontal cortex and striatum. It comes in immediate-release and extended-release (ER) formulations. Optimal dosing is achieved through titration of the medication by a trained physician. Its use for the treatment of ADHD in young people with ADHD and autism has been supported by research.[248] Methylphenidate can be associated with significant headache, loss of appetite, abdominal discomfort, nausea, anxiety and insomnia. Side effects are dose dependent and require monitoring.

R 4.1 ***Methylphenidate should be considered as the first line pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents on the autism spectrum. Any treatment plan should include non-pharmacological approaches. [EM4-1]***

4.1.1.2 Atomoxetine

Atomoxetine is a non-stimulant drug approved for the treatment of ADHD in individuals on the autism spectrum. A small meta-analysis showed that atomoxetine improved symptoms of ADHD in children and adolescents on the autism spectrum.[249] A study using atomoxetine in patients on risperidone also showed some improvements in behaviour.[250] Atomoxetine was associated with significant nausea, appetite loss and mood-related side effects that were tolerated by most patients.

R 4.2 ***Atomoxetine may be considered for managing attention deficit hyperactivity disorder in children and adolescents on the autism spectrum if methylphenidate has been tried unsuccessfully or is contraindicated/not tolerated. [EM4-2]***

4.1.1.3 *Alpha-2 Adrenergic Receptor Agonists*

Guanfacine and clonidine are alpha-2 adrenergic receptor agonists which are off-label treatments for ADHD. Since publication of the last guideline, there has been no new research on clonidine.

Two related papers from one randomised controlled trial (RCT) showed that guanfacine had a significant impact on hyperactivity and inattention in children with both autism and ADHD.[251,252] The numbers treated were small, and those treated with guanfacine were found to have gastrointestinal symptoms, somnolence, challenging behaviour, dry mouth and decreased appetite. Further studies are needed to replicate this.

R 4.3 ***Guanfacine may be considered for managing attention deficit hyperactivity disorder in children and adolescents on the autism spectrum after methylphenidate and atomoxetine have been tried unsuccessfully or if they are contraindicated. [EM4-6]***

4.1.2 Challenging Behaviours and Psychiatric Conditions

4.1.2.1 Antipsychotics

Risperidone is a second-generation antipsychotic that has an affinity for dopamine (D2), serotonin (5-HT2A), adrenergic (alpha 1, alpha 2) and histamine (H1) receptors. The mechanism of action of risperidone is not fully understood; current theories focus mainly on its ability to block D2 and 5-HT2A receptors. Aripiprazole is a second-generation antipsychotic that acts as a partial D2 agonist, partial 5HT-1A agonist and 5HT-2A antagonist. Risperidone and aripiprazole are approved by the US Food and Drug Administration (FDA) for the treatment of irritability and aggression in children (from the age of 5 for risperidone and the age of 6 for aripiprazole).

Systematic reviews addressing the effects of risperidone in children on the autism spectrum have provided evidence of its efficacy in the treatment of irritability, as well as suggestive evidence for reduction of repetitive behaviours.[253,254] Three RCTs also provided strong evidence for the short-term efficacy of aripiprazole in reducing irritability, hyperactivity and stereotypies in autistic children.[255–257] There is high certainty of evidence (low to moderate risk of bias) for risperidone and aripiprazole improving challenging behaviours in the short term (less than 6 months). Behaviours were noted to improve in the longer term (≥6 months) when both these antipsychotics were used compared with placebo; however, confidence in this conclusion is low (low strength of evidence) as only five studies had ≥6 months follow-up. Network meta-analysis showed comparable efficacy and safety profile of risperidone and aripiprazole. Both medications have the propensity to cause somnolence and weight gain.

There was inadequate data to assess effects of risperidone when used in conjunction with adjunctive agents (amantadine, buspirone, celecoxib, memantine, riluzole, Gingko biloba, pioglitazone, or topiramate) on any outcomes assessed as there was no study that addressed the same adjunctive agent (insufficient strength of evidence). There were two RCTs that addressed risperidone used in conjunction with N- acetylcysteine but the data was inadequate to comment on effects given the small number of participants and high attrition rate.

There is limited or no recent RCT data on the efficacy of other antipsychotics (mostly open-label studies, retrospective chart analysis and case series/reports).

R 4.4 ***Risperidone and aripiprazole can be used for challenging behaviours (irritability and hyperactivity) in children and adolescents on the autism spectrum in the short term. There is insufficient evidence to conclude that risperidone and aripiprazole are beneficial in the long term (more than 6months). Both risperidone and aripiprazole can cause weight gain and somnolence. [EM4-4]***

4.1.2.2 Selective Serotonin Re-uptake Inhibitors (SSRIs)

SSRIs are a class of antidepressant medication commonly used in psychiatric practice for the treatment of anxiety, depression and obsessive-compulsive disorder. SSRI treatment leads to increased activation of serotonergic brain systems. There is a black box warning (FDA 2004) for its use in children and adolescents due to its association with an increased risk of suicidal thinking, feeling and behaviour in young people.

A Cochrane review indicated that SSRIs were of limited benefit in children and adolescents on the autism spectrum.[258] Citalopram was found to be associated with significant harm in children on the autism spectrum. Decisions about the use of SSRIs (evidence favours fluoxetine and fluvoxamine) in the treatment of children and adolescents on the autism spectrum diagnosed with co-occurring anxiety, depression and obsessive-compulsive disorder should be made on a case-by-case basis by an appropriately trained specialist.

R 4.5 ***SSRIs (e.g., fluoxetine, fluvoxamine, sertraline, escitalopram, citalopram, paroxetine) should not be used for the treatment of core symptoms of autism in children and adolescents. SSRIs may be used to treat psychiatric conditions (e.g., anxiety, depression, OCD) in consultation with an appropriately trained specialist. [EM4-5]***

4.1.2.3 *Tricyclic Antidepressants (TCAs)*

TCAs inhibit presynaptic reuptake of norepinephrine and serotine, and also block cholinergic, histaminergic, alpha1-adrenergic and serotonergic receptors, leading to unwanted side effects. Apart from treating major depression, they have also been used for obsessive-compulsive disorder, panic disorder, and pain management. However, their use has diminished greatly due to the availability of other antidepressants with better side effect profiles and which are safer in overdose.

A Cochrane review included three small trials examining the use of two TCAs – clomipramine and tianeptine.[259] The results from the clomipramine trials were conflicting, showing improvement for autistic symptoms, irritability and obsessive-compulsive disorder type symptoms, conflicting results for hyperactivity and no improvement on inappropriate speech. Tianeptine did not produce significant improvement for irritability, hyperactivity, eye contact, or inappropriate speech. Excessive drowsiness and reduced activity levels were observed from the tianeptine group, and a higher discontinuation rate was also reported from one of the clomipramine trials.

R 4.6 ***TCAs (e.g., clomipramine, tianeptine) should not be used for the management of challenging behaviours in children and adolescents on the autism spectrum. TCAs may be considered as a second- or third-line option to treat psychiatric conditions (e.g., depression) in consultation with an appropriately trained specialist. [EM4-6]***

4.1.2.4 *Anticonvulsants*

Anticonvulsants, namely valproic acid, lamotrigine, levetiracetam, topiramate, and oxcarbazepine are used as mood stabilisers and, together with lithium, have been examined in children and adolescents on the autism spectrum.

A systematic review and meta-analysis of seven double-blind RCTs (n=171) showed no significant benefit of valproic acid (alone or with fluoxetine), lamotrigine, levetiracetam and topiramate (with risperidone) for the management of challenging behaviours compared to placebo.[260] The use of levetiracetam appeared to improve behavioural and cognitive functions in autism with subclinical epileptiform discharges.[261] There are only very small case reports describing the use of oxcarbazepine in improving irritability/agitation in autism, and the use of lithium for manic/euphoric symptoms. There is therefore *insufficient evidence* to support the use of valproic acid, lamotrigine, levetiracetam, topiramate, oxcarbazepine and lithium to treat challenging behaviours in children and adolescents on the autism spectrum.

R 4.7 ***Anticonvulsants/mood stabilisers should not be routinely used for the management of challenging behaviours in children and adolescents with autism. They may be considered as a second- or third-line option to treat challenging behaviours or psychiatric conditions in children and adolescents on the autism spectrum, in consultation with an appropriately trained specialist. [EM4-7]***

4.1.2.5 *Mirtazapine*

Mirtazapine is a tetracyclic antidepressant that increases the release of norepinephrine and serotonin by antagonizing presynaptic alpha2-adrenergic and serotonin (5HT2 and 5-HT3) receptors. It is licensed for use in major depression. There is limited evidence from case reports and open-label studies to suggest improvements in aggression, self-injurious behaviour, irritability, hyperactivity, anxiety, depression, insomnia and sexually-inappropriate behaviours with mirtazapine.[254] A small, pilot RCT showed some positive trends in improving anxiety in children and adolescents on the autism spectrum.[262] Moreover, recent case reports agree with previous reports that mirtazapine helps to

improve severe restricted and repetitive behaviours and inappropriate sexual behaviours. Improvements in appetite, sleep, irritability and aggression have also been reported. The use of mirtazapine appears to be well tolerated, adverse effects are generally mild and transient and include increased appetite, irritability and transient sedation. However, there is still *insufficient evidence* to recommend the use of mirtazapine for the management of anxiety or challenging behaviours in children and adolescents on the autism spectrum.

R 4.8 ***Mirtazapine should not be routinely used for the management of challenging behaviours in children and adolescents with autism. It may be considered as a second- or third-line option to treat anxiety in children and adolescents on the autism spectrum, in consultation with an appropriately trained specialist. [EM4-8]***

4.1.2.6 *Buspirone*

Buspirone is a novel anxiolytic agent and acts as a serotonin 5-HT1A receptor agonist. Buspirone is approved by the US FDA for treatment of anxiety disorders, such as generalised anxiety disorder.

One small double-blind RCT evaluated buspirone or placebo in addition to risperidone for challenging behaviours in children on the autism spectrum.[263] More children receiving buspirone and risperidone had a ≥30% reduction in irritability score than those receiving placebo and risperidone. However, the study was noted to have a relatively high risk of bias, indirectness and imprecision, leading to the certainty of evidence being very low. Another retrospective chart review showed improvements in anxiety symptoms in children with lower support needs.[264] Overall, there is *insufficient evidence* for the use of buspirone in children and adolescents on the autism spectrum.

R 4.9 ***Buspirone should not be used as an adjunct with risperidone for the treatment of challenging behaviours in children and adolescents on the autism spectrum. [EM4-9]***

4.1.2.7 *Celecoxib*

The mechanism of action of celecoxib is due to selective inhibition of cyclooxygenase-2 (COX-2), which is responsible for prostaglandin synthesis, an integral part of the pain and inflammation pathway. This pharmacologic activity gives celecoxib its analgesic, anti-inflammatory, and antipyretic effects.

There is only one small double-blind placebo-controlled RCT exploring the effectiveness of adding celecoxib as an adjunct to risperidone versus placebo plus risperidone in 40 children on the autism spectrum.[265] This reported significant improvements in irritability, lethargy/social withdrawal, and stereotypy in the celecoxib group compared with placebo. Although of moderate quality, the study population is very small, and there is therefore overall low strength of evidence for adjunct use of celecoxib with risperidone in improving challenging behaviour in autism. Overall, there is *insufficient evidence* for the use of celecoxib in children and adolescents on the autism spectrum.

R 4.10 ***Celecoxib should not be used as an adjunct with risperidone for the treatment of challenging behaviours in children and adolescents on the autism spectrum. [EM4-10]***

4.1.2.8 *Galantamine*

Galantamine is a cholinesterase inhibitor with a dual mechanism of action. It is a reversible inhibitor of acetylcholine esterase and enhances the intrinsic action of acetylcholine on nicotinic receptors, leading to increased cholinergic neurotransmission in the central nervous system.

One small double-blind RCT evaluating galantamine or placebo in addition to risperidone was conducted in 40 autistic children.[266] Children in the galantamine adjunct group showed significantly greater improvement in ABC Irritability and Lethargy/Social Withdrawal subscales than the placebo group. There is low risk of bias in this study, but it is the only small RCT that has studied the benefits of adjunct use of galantamine with risperidone. There is therefore *insufficient evidence* for the adjunct use of galantamine with risperidone in improving challenging behaviours in autism.

R 4.11 ***Galantamine should not be used as an adjunct with risperidone for the treatment of challenging behaviours in children and adolescents on the autism spectrum. [EM4-11]***

4.1.3 Sleep Difficulties

4.1.3.1 *Melatonin*

Melatonin is an endogenous hormone produced by the pineal gland that regulates sleep-wake cycles and, when provided exogenously, has beneficial effects on sleep-onset latency. It is available as an over-the-counter supplement.

There are two RCTs that have studied the effect of immediate release melatonin[267,268] and another two RCTs that have studied the effects of controlled/prolonged release melatonin.[269,270] There was moderate quality of evidence that immediate-release melatonin improves sleep latency, and that controlled/prolonged release melatonin improves sleep latency and total sleep time in children on the autism spectrum. An earlier meta-analysis conducted in 2011 (five double-blind RCTs) showed a large effect size, favouring melatonin, in sleep duration and sleep-onset latency.[271] A meta-analysis of behavioural interventions, including three RCTs, also found significant effects in terms of improving sleep. There is therefore moderate strength of evidence (low to moderate risk of bias) for melatonin improving sleep issues in children on the autism spectrum.

R 4.12 ***Melatonin can be considered for sleep issues if there is no benefit from a psychosocial intervention. It should be used in conjunction with a psychosocial intervention and in consultation with a specialist trained in assessing and managing sleep issues in children and adolescents on the autism spectrum. [EM4-12]***

4.2 PHARMACOLOGICAL AGENTS TARGETING CORE SYMPTOMS OF AUTISM

4.2.1 Glutamatergic and Gamma-aminobutyric Acid (GABA)ergic Agents

Autism is associated with multiple neurotransmitter abnormalities including amino acid neurotransmitters (i.e., glutamate, γ-aminobutyric acid [GABA]).[272] It is postulated that autism is a result of an increased ratio of excitation to inhibition during key stages of development, either from too much excitation, too little inhibition or a combination of both. As such, pharmacological agents targeting glutamate, the main excitatory neurotransmitter, and GABA, the main inhibitory neurotransmitter, may be of benefit to individuals on the autism spectrum.

4.2.1.1 *Acamprosate*

Acamprosate is a drug used for the maintenance of abstinence from alcohol in adults. It binds at the N-methyl-D-aspartate (NMDA) glutamate receptor, enhancing activation at low glutamate concentrations and inhibiting receptor activation at high glutamate concentrations. Acamprosate also acts as an antagonist at metabotropic glutamate receptors (mGluRs), blocks the neurotoxic effects of the mGluR agonist trans-ACPD, and has agonist effects at GABA(A).

An open-label pilot study of acamprosate showed improvement in social relatedness on the Social Responsiveness Scale for 5 out of 6 youth on the autism spectrum.[273] In a further single-blind placebo lead-in trial, 6 of 9 individuals on the autism spectrum who received active treatment were deemed treatment responders on the Clinical Global Impressions Improvement and Aberrant Behaviour Checklist Social Withdrawal subscale.[274] No double-blind RCTs on acamprosate in autism have been conducted to date.

Acamprosate was generally well tolerated. Adverse effects included loose bowel movements, reduced appetite, mild nausea, headache, insomnia, irritability and tiredness.

Currently, there are no good-quality studies directly examining the effects of acamprosate on the core symptoms of autism in children and adolescents and hence *insufficient evidence* that acamprosate has significant effects on core symptoms of autism.

R 4.13 ***Acamprosate should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-13]***

4.2.1.2 *Amantadine*

Amantadine is a non-competitive NMDA receptor antagonist, binding to it to avoid its excessive excitation by the glutamate neurotransmitter. It also increases synaptic dopamine and has been shown to reduce problem behaviours related to executive dysfunction.

A randomised double-blind, placebo-controlled trial evaluating amantadine's effects on aberrant behaviour in 39 youth on the autism spectrum showed a statistically significant decrease in hyperactivity and inappropriate speech with amantadine versus placebo on clinician ratings, but not on parent report. There was moderate to marked improvement on Clinical Global Impression of Improvement (CGI-I) scores in 53% of youths on amantadine compared to placebo (25%).[275] Another double-blind, randomised, placebo-controlled trial evaluated adjunctive amantadine to risperidone in 40 severely disruptive children on the autism spectrum. Clinician-rated Aberrant Behavioural Checklist-Community (ABC-C) showed a statistically significant decrease in irritability and hyperactivity/ noncompliance items with amantadine versus placebo after 10 weeks.[276]

Reported adverse effects include insomnia and antisocial behaviour. However, these effects were not statistically significant.

Currently, there are *insufficient studies* examining the effects of amantadine on the core symptoms of autism, and as an adjunct to risperidone in the treatment of irritability in autism.

R4.14 ***Amantadine should not be used for the treatment of core symptoms of autism in children and adolescents. Amantadine should also not be used as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum. [EM4-14]***

4.2.1.3 *Arbaclofen*

Arbaclofen is a GABA receptor type B agonist. It also acts presynaptically to reduce glutamate release and may thus have a mechanism that converges with that of mGluR5 antagonists.

In an 8-week open-label trial of arbaclofen in 32 children and adolescents on the autism spectrum, improvements were observed on several outcome measures including the ABC-Irritability and the Lethargy/Social Withdrawal subscales, the Social Responsiveness Scale, the CY-BOCSPDD, and clinical global impression scales.[277] A randomised, placebo-controlled, phase 2 study of arbaclofen was conducted in 150 autistic participants, aged 5–21 years. No difference from placebo was detected on the primary outcome measure, the parent-rated Aberrant Behaviour Checklist Social Withdrawal/Lethargy subscale. However, improvements were seen in the clinician-rated Clinical Global Impression of Severity and in the Vineland Adaptive Behaviour Scales II socialization domain in participants receiving arbaclofen.[278]

Arbaclofen was generally well tolerated. The most common adverse effects include vomiting (15.8%), upper respiratory infection (13.2%), affect lability (10.5%) and headache (10.5%).

There are ongoing plans for further trials investigating whether arbaclofen is superior to placebo in autism in improving social function and other secondary outcomes over 16 weeks, along with safety and tolerability profiles.[279]

Currently, there are *insufficient studies* examining the effects of arbaclofen on the core symptoms of autism in children and adolescents.

R 4.15 ***Arbaclofen should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-15]***

4.2.1.4 *Bumetanide*

The neurotransmitter GABA exerts inhibitory actions in the adult nervous system. In the developing foetus, GABA exhibits excitatory activity during normal central nervous system development. The persistence of excitatory GABA neuronal signalling with high intracellular chloride levels has been found in individuals on the autism spectrum. The Na-K-Cl cotransporter 1 (NKCCl) imports chloride, resulting in increased intracellular chloride levels, neuronal depolarization and excitatory GABA effects. Bumetanide, a loop diuretic and an NKCCl antagonist, has been proposed as a potential treatment for the behavioural symptoms of autism in view of its action of decreasing intracellular chloride and reducing aberrant GABA excitatory signalling.[280,281]

Open-label trials with bumetanide have been conducted in individuals on the autism spectrum ranging from infancy to young adulthood. Results have suggested improvements in core autism symptomatology, behavioural difficulties, emotional regulation, repetitive behaviours, emotional recognition, eye contact, communicative and cognitive abilities and overall function.[282–285]

Five RCTs have been conducted to date. Lemonnier et al. (2017) conducted a double-blind trial of bumetanide on 60 children on the autism spectrum and observed improvements on measures of autism severity.[286] Further investigation was done with 88 autistic individuals randomised to bumetanide and placebo with similar observed improvements in core autism symptomatology.[287] Du et al. (2015) investigated the therapeutic effects of combined bumetanide and applied behaviour analysis (ABA) treatment in 60 children on the autism spectrum and concluded that treatment with bumetanide combined with ABA training could result in a better outcome than ABA training alone.[288] Zhang et al. (2020) correlated neuroimaging findings with clinical measures in a study of 83 autistic individuals randomised into bumetanide and control groups. Participants in the bumetanide group demonstrated alleviation of core autism symptoms associated with reduction in inhibitory GABA to excitatory glutamate ratio on magnetic resonance spectroscopy.[289] In the most recent BAMBI (Bumetanide for Core Symptoms of Autism Spectrum Disorder) trial, 92 participants were randomised to bumetanide or placebo group. Bumetanide was not found to be superior to placebo in measures of autism symptomatology on the Social Responsiveness Scale-2 but a superior effect was found on the Repetitive Behaviour Scale Revised.[290]

Bumetanide was generally well tolerated. Adverse effects experienced included polyuria/pollakiuria, mild hypokalaemia, orthostatic hypotension, dehydration, loss of appetite, fatigue and hyperuricemia.

There are two upcoming Phase III studies evaluating the efficacy/safety of bumetanide oral liquid formulation in autism. These are international, multicentre, randomised, double-blind, placebo-controlled studies in children and adolescents on the autism spectrum aged 7 to 17 years (n=200; study 1), or younger children on the autism spectrum aged 2 to 6 years (n=200; study 2). The primary endpoint of each is change in Childhood Autism Rating Scale 2 total raw score after 6 months.[291]

There are now several RCTs examining the effects of bumetanide on the core symptoms of autism in children and adolescents. While the findings of some studies are promising, some of the studies are not sufficiently rigorous. The most recent and largest study, the BAMBI trial, did not demonstrate benefit of bumetanide in measures of social communication in comparison with placebo and findings are hence not consistent.

R 4.16 ***Based on current evidence, bumetanide should not be used for the treatment of core symptoms of autism in children and adolescents. Further results from clinical trials on bumetanide are awaited. [EM4-16]***

4.2.1.5 *D-cycloserine*

D-cycloserine exerts a partial agonistic action at NMDA glutamate receptors NR1/NR2C at low doses, and antagonistic action on NR1/NR2A and NR1/NR2B receptors at high doses. NMDA receptors are responsible for sociability, and diminished NMDA receptor–mediated activity is associated with impaired sociability. As such, low dose D-cycloserine acting as an NMDA receptor agonist, has been considered in the treatment of autism to improve social and communication skills.

A recent Cochrane review[292] included a single randomised controlled trial of 67 children on the autism spectrum aged between 5 and 11 years who were randomised to receive either 10 weeks of D-cycloserine plus social skills training or placebo plus social skills training.[293] There was little to no difference between the two groups for all outcomes (social interaction or communication difficulties, restricted, repetitive, stereotyped patterns of behaviour, non-core symptoms of autism, serious adverse events and tolerability of D-cycloserine) measured at one week post-treatment.

Adverse effects reported include headache, nasal congestion, cough and emesis with adverse effects being more common than in the placebo group, although this difference was not significant.

Currently, there is only one study examining the effects of D-cycloserine as an adjunct to social skills training on the core symptoms of autism in children. Results suggest no differences in effects as compared to placebo.

R 4.17 ***D-cycloserine should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-17]***

4.2.1.6 *Memantine*

Memantine is a pharmacological agent which is used in the treatment of dementia. It acts as a non-competitive antagonist of glutamatergic NMDA type receptors. It inhibits pathological overactivation, neuroexcitation and cell death of NMDA receptor cells by glutamate, thereby ameliorating the clinical symptoms of autism.[294,295]

Open-label trials with memantine on autistic populations found improvements in measures of autism severity and symptoms of social withdrawal, language, inattention, hyperactivity, anxiety, lethargy, irritability and memory.[296]

Memantine has been compared against risperidone in a randomised trial comprising 30 children on the autism spectrum. Comparable improvements for both drugs were noted in measures of aberrant behaviours and autism severity.[297] Another randomised, double-blind placebo-controlled pilot trial evaluated the neurocognitive effects of memantine over a 24-week period with 23 children and found improvements in verbal recognition memory.[298]

Memantine has also been investigated as an adjunctive treatment. An RCT examined the effects of memantine plus risperidone against placebo plus risperidone and found that the group that received memantine had greater reduction in measures for irritability, stereotypic behaviour and hyperactivity.[299] Another randomised, single-blind clinical trial divided 60 children on the autism spectrum undergoing ABA into two groups of memantine and placebo and found that post intervention, both groups showed improvements in scores of autism severity, with only the scores in the memantine group showing significant improvement.[300]

However, more systematic trials have failed to show significant efficacy of memantine. In a pharmaceutical company-funded randomised, placebo-controlled, proof-of-concept, phase I–II study with an open-label extension, the efficacy, safety, and tolerability of memantine ER in children on the autism spectrum was investigated. Findings suggested no significant between-group differences on measures of social communication although memantine was well-tolerated.[294] The study continued with three phase II trials (an open-label trial; a randomised, double blind, placebo-controlled withdrawal trial; and an open-label extension trial) conducted to assess the efficacy and long-term safety of memantine

in the autistic population. Findings suggested that treatment with memantine-ER in the double-blind, placebo-controlled trial failed to demonstrate meaningful differences in efficacy between memantine and placebo.[295]

Currently, findings are inconsistent and weak on the effects of memantine on the core symptoms of autism in children and adolescents. There are insufficient studies examining the use of memantine as an adjunct to risperidone in the treatment of irritability in autism.

R 4.18 ***Memantine should not be used for the treatment of core symptoms of autism in children and adolescents. Memantine should also not be used as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum. [EM4-18]***

4.2.1.7 N-acetylcysteine

N-Acetylcysteine (NAC) is the N-acetyl derivative of L-cysteine used in treatment of acetaminophen overdose, as a mucolytic in chronic obstructive pulmonary disease, and as a renal protectant in contrast-induced nephropathy.[301] It is an antioxidant with glutamatergic action, thus potentially acting on two different proposed pathophysiological mechanisms of autism.[302]

Glutathione is one of the most important antioxidants in the human body. Studies have consistently reported glutathione deficiency in autism.[303] NAC replenishes cysteine, the rate-limiting agent in glutathione synthesis.

L-cysteine in NAC is oxidised to cystine in the brain which is a substrate for the glutamate-cystine antiporter. This then facilitates the cellular uptake of cystine, which causes the reverse transport of glutamate into the extracellular space thus decreasing glutamatergic neurotransmission and the E:I ratio.

In a recent meta-analysis of five randomised controlled trials, the authors concluded that NAC is safe and tolerable, reduces hyperactivity and irritability and enhances social awareness in children on the autism spectrum. However, it was suggested that further evidence was needed before a general recommendation could be made.[304] A further mixed-method analysis of one of the five randomised controlled trials was reported based on parents' assessment reports, professionals' observations, and researchers' detailed case notes. Results supported the usefulness of NAC in children on the autism spectrum for treating potentially disruptive behaviour (e.g., aggression and hyperactivity) and improving verbal communication.[305]

Two studies compared the effect of different doses of NAC as an adjunctive therapy to risperidone versus placebo plus risperidone in a total of 80 children with autistic disorder.[306,307] By the end of the treatment, the NAC groups had significantly greater reduction in irritability scores than the placebo group in both the trials. In one RCT, scores on the hyperactivity/noncompliance subscales were also significantly improved in the NAC group. Other subscale scores did not differ between groups in either RCT. Adverse events were mild and transient, with a similar incidence in both trials.

Evidence on the effects of NAC on core symptoms of autism is inconsistent and inconclusive. There is also inadequate evidence to comment on effects of NAC plus risperidone in the treatment of irritability, given the small number of participants, high attrition and short-term nature of the studies.

R 4.19 ***N-acetylcysteine should not be used for the treatment of core symptoms of autism in children and adolescents. There is currently insufficient evidence for the use of N-acetylcysteine as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum and further studies need to be conducted. [EM4-19]***

4.2.1.8 *Riluzole*

Riluzole is an anti-glutamatergic agent used in the treatment of amyotrophic lateral sclerosis.[308] Riluzole inhibits glutamate production, reduces glutamic acid release, and enhances glutamate synaptic uptake. Riluzole also interacts with inhibitory neurotransmitters, increasing the depolarizing effect of GABA and enhancing GABAergic inhibitory function.

Three studies have examined the effects of riluzole in autism to date. An RCT examined the efficacy and tolerability of riluzole as an adjunctive to risperidone in the treatment of irritability in autistic children. Forty children aged 5–12 years with a diagnosis of autistic disorder were enrolled and received riluzole or placebo in addition to risperidone for 10 weeks. A significantly greater improvement in the ABC-C irritability subscale score was achieved by the riluzole-treated children compared with the placebo group. Patients in the riluzole group also showed significantly greater improvement on the lethargy/social withdrawal, stereotypic behaviour, and hyperactivity/non-compliance subscales. However, children receiving riluzole experienced significant increases in their appetite and body weight.[309]

In an unpublished study, long-term monotherapy of riluzole was found to result in the reduction of irritability and hyperactivity.[310] Another 12-week randomised, double-blind, placebo-controlled, crossover pilot study evaluated the safety and tolerability of adjunctive riluzole against placebo in adolescents and young adults. While riluzole was well tolerated, there was no observed effect on target symptoms on the Clinical Global Impression Improvement Scale or the Aberrant Behaviour Checklist Irritability subscale.[311]

Currently, there are *insufficient studies* directly examining the effects of riluzole on the core symptoms of autism in children and adolescents.

There is one study addressing the effects of riluzole as an adjunct to risperidone in the treatment of irritability in autism. However, the study is small with no other study replicating similar findings.

R 4.20 ***Riluzole should not be used for the treatment of core symptoms of autism in children and adolescents. Riluzole should also not be used as an adjunct with risperidone for the treatment of irritability in children and adolescents on the autism spectrum. [EM4-20]***

4.2.2 Other Drugs

Within this category of Other Drugs, the evidence for drugs targeting a variety of other mechanisms thought to be involved in the pathogenesis of autism is presented. As autism primarily affects social communication and social interaction, neural pathways involved in social behaviours have been researched in attempts to identify potential therapeutic targets for core symptoms of autism. Key social hormones in mammals include oxytocin and arginine vasopressin. Apart from these, research in subgroups of individuals with genetic conditions known to have a strong predisposition for the development of autism (e.g., Rett syndrome, tuberous sclerosis (TS) and Fragile X syndrome (FXS)) have led some to explore targeted therapies in pathways known to be affected in these conditions. Such drugs would include insulin-like growth factor 1 (IGF-1), mTOR inhibitors and metformin. Finally, other drugs with known psychotropic effects to treat dementia (cholinesterase inhibitors) or epilepsy (cannabinoids) have also been studied for their potential use in autism, together with miscellaneous agents like suramin and naltrexone.

4.2.2.1 Oxytocin

Oxytocin is a neuropeptide hormone that acts as a neurotransmitter. Apart from stimulating uterine contractions during childbirth, it also plays an important role in social bonding, facilitating trust and attachment. A recent systematic review also shows associations between oxytocin receptor (*OXTR*) gene polymorphisms and social, emotional or behavioural functioning in children and adolescents, including autism.[312] However, despite promising results from early animal studies on oxytocin as a

potential treatment for autism, the results from clinical trials to date have been disappointing and heterogenous,[313] with no clear evidence for efficacy. Several trials on intranasal oxytocin as a treatment for autism are currently ongoing (Japan (NCT03466671, RCT), China (NCT03610919, RCT) and USA (NCT02985749, open-label), as well as one locally). Until further results are available, there is currently *insufficient evidence* to support the use of intranasal oxytocin as a treatment for core autism symptoms in children and adolescents.

R 4.21 ***Based on current evidence, intranasal oxytocin should not be used for the treatment of core symptoms of autism in children and adolescents. Further results from clinical trials on oxytocin are awaited. [EM4-21]***

4.2.2.2 Vasopressin 1a Receptor (V1a) Antagonist (balovaptan)

Balovaptan is a small molecule that potently and selectively antagonises the V1a receptor in the central nervous system. Following animal model studies suggesting that V1a receptor inhibition could improve social behaviours, various clinical trials have been conducted on balovaptan in adults with autism but have failed to show any improvements in social symptoms,[314,315] leading to early termination of one trial on grounds of futility.[316] Only one trial has been conducted in children and published as a conference abstract,[317] indicating a similar lack of efficacy. As a result, there is current evidence that balovaptan is *ineffective* as a treatment for core autism symptoms in both adults and children.

R 4.22 ***Balovaptan should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-22]***

4.2.2.3 Insulin-like Growth Factor 1 (IGF-1) (trofinetide, mecasermin)

IGF-1 is a polypeptide hormone that exerts effects on development, growth and maturation of cells, including neural cells. In animal studies on the MECP2 variant (which results in Rett Syndrome in humans), administration of IGF-1 was found to reverse phenotypic features of Rett Syndrome.[318] After IGF-1 came into clinical use for the treatment of severe growth failure and IGF-1 deficiency in children, it has also been studied in clinical trials for conditions associated with autism, such as Rett syndrome,[319] Phelan-McDermid syndrome,[320] and FXS.[321] However, the overall quality of evidence is very low, and it has yet to be studied for use in autistic children who do not have these associated genetic conditions. Clinicaltrials.gov indicates one ongoing double-blind, placebo-controlled crossover trial in the USA, recruiting only 10 autistic children to evaluate IGF-1 (mecasermin) on core symptoms (NCT01970345). Therefore, there is currently *insufficient evidence* for the use of IGF-1 to treat core autism symptoms in children and adolescents.

R 4.23 ***Insulin-like growth factor 1 (IGF-1; e.g., trofinetide, mecasermin) should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-23]***

4.2.2.4 mTOR Inhibitors (everolimus, rapamycin)

There has been research into the possible use of mammalian target of rapamycin (mTOR) inhibitors for the treatment of TS, following the discovery that two causative genes of TS (TSC1 (chromosome 9q34) and TSC2 (16p13.3)) are located at the crossroad midstream of the mTOR pathway. Defects in these genes result in cerebral cortical dysgenesis, intractable epilepsy, intellectual disability, and/or autism.[322] mTOR inhibitors have recently been proven to be effective for treating epilepsy in human TS patients,[323] and for autism phenotypes in TS mouse models. Despite this, the literature on human trials for autism is very limited and disappointing to date,[324,325] with no significant benefits found and a concerning adverse effect profile. Therefore, there is currently *insufficient evidence* for the use of mTOR inhibitors to treat core autism symptoms in children and adolescents.

R 4.24 ***mTOR inhibitors (everolimus, rapamycin) should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-24]***

4.2.2.5 *Metformin*

Metformin is a biguanide mainly used for the treatment of type 2 diabetes mellitus. Pre-clinical studies showed that metformin corrected social and repetitive behaviours in a mouse model of FXS, and a case series on seven individuals with FXS (of which 2 were children) showed some improvement in behaviour scores using the Aberrant Behaviour Checklist.[326] However, other existing clinical trials have focused mainly on the treatment of antipsychotic-induced weight gain in children and adolescents with autism,[327–329] and not the evaluation of the core symptoms of autism. A search on Clinicaltrials.gov only yielded ongoing double-blind RCTs on metformin for individuals with FXS aged between 6 years to adulthood in the USA (NCT03479476), and Canada (NCT03862950), and a planned prospective cohort study on metformin on social behaviour in adults with autism in Switzerland (NCT04930471). Hence there is *insufficient evidence* for the use of metformin to treat core autism symptoms in children and adolescents.

R 4.25 ***Metformin should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-25]***

4.2.2.6 *Cholinesterase Inhibitors (donepezil, galantamine, rivastigmine)*

Abnormalities of the cholinergic system in autism have been implicated via histological, functional imaging, and functional gene analyses studies in humans and in animal studies.[330] Cholinesterase inhibitors such as donepezil, galantamine and rivastigmine are licensed for use in Alzheimer's dementia in Singapore. However, small clinical trials on donepezil for treating autism in children have failed to show any improvements in core symptoms.[330,331] One small double-blind RCT on galantamine in children on the autism spectrum showed improvements in social withdrawal and irritability scores on the ABC-C, but galantamine was used as an augmentative treatment to risperidone.[266] Hence there is *insufficient evidence* that cholinesterase inhibitors have a beneficial effect on core symptoms of autism in children and adolescents.

R 4.26 ***Cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) should not be used for the routine treatment of core symptoms of autism in children and adolescents. There may be grounds for further well-designed clinical trials on galantamine for treating core symptoms of autism in children and adolescents. [EM4-26]***

4.2.2.7 *Cannabinoids*

With the legalisation of cannabinoids in various countries for the treatment of various medical conditions such as amyotrophic lateral sclerosis, cancer, chronic non-cancer pain, severe epilepsy, and multiple sclerosis, publications on the possible use of cannabinoids for treating autism started to emerge in the 2010s. Individuals with autism can exhibit features of irritability, anxiety, aggressiveness and hyperactivity, which are sometimes not responsive to standard medical and behavioural treatment.[332,333] However, there has only been one double-blind RCT on cannabidiol in children on the autism spectrum that concluded that evidence for efficacy was mixed and insufficient,[334] despite other previous open-label, uncontrolled studies reporting overall improvements. Although Clinicaltrials.gov shows two new or ongoing trials in children on the autism spectrum (NCT05212493 – open label, NCT03202303 - RCT), there currently remains *insufficient evidence* for the use of cannabinoids to treat core autism symptoms in children and adolescents.

R 4.27 ***Cannabinoids should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-27]***

4.2.2.8 *Miscellaneous Drugs*

Suramin is a phenylurea that acts as an inhibitor of purinergic signalling and is used to treat trypanosomiasis. Following some mouse model experiments indicating possible improvements in autism-like symptoms, two small trials have been conducted in children on the autism spectrum. Although the first pilot of only 10 children showed a small improvement in ADOS comparison scores,[335]

the second larger trial in 52 children (published as an abstract only) showed no significant benefits over placebo.[336] Therefore, there is currently *insufficient evidence* for the use of suramin to treat core autism symptoms in children and adolescents.

R 4.28 ***Suramin should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-28]***

Naltrexone was investigated for the treatment of autism after researchers noted that some symptoms of autism resembled behaviours induced by opiate administration, such as reduced socialisation, insensitivity to pain, and repetitive stereotypies.[337] It was postulated that autism symptoms might be due to dysfunction in the pineal hypothalamic–pituitary–adrenal axis leading to over-secretion of opioid peptides and serotonin. However, following a flurry of small clinical trials in the 1990s-2001 which indicated *insufficient evidence* of any effect of naltrexone on core symptoms of autism in children,[338] there have been no further trials since.

R 4.29 ***Naltrexone should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-29]***

Piracetam is a racetam which has some effect on AMPA-sensitive glutamate receptors, but not on GABA. There has only been one small double-blind placebo-controlled trial of piracetam as an adjunct to risperidone for treating children on the autism spectrum published in 2008. However, there have been no studies since, and none on piracetam alone.[339]

R 4.30 ***Piracetam should not be used for the treatment of core symptoms of autism in children and adolescents. [EM4-30]***

Abbreviations

ABA, applied behavioural analysis; ABC-C, Aberrant Behavioural Checklist-Community; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BAMBI, Bumetanide for Core Symptoms of Autism Spectrum Disorder; CGI-I, Clinical Global Impression of Improvement; COX-2, cyclooxygenase-2; ER, extended-release; FDA, Food and Drug Administration; FXS, Fragile X syndrome; GABA, γ-aminobutyric acid; IGF-1, insulin-like growth factor 1; mTOR, mammalian target of rapamycin; NAC, N-acetylcysteine; NKCC1, Na-K-Cl cotransporter 1; NMDA, N-methyl-D-aspartate; OXTR, oxytocin receptor; RCT, randomised controlled trial; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant; TS, tuberous sclerosis.

CHAPTER 5: EDUCATION AND TRANSITION

5.1 THE COMPULSORY EDUCATION (CE) ACT

The Compulsory Education Act (CE Act) was revised in 2019 to include children with moderate-to-severe special educational needs. It stipulates that all children who are Singapore Citizens (SC) residing in Singapore and of compulsory school age (i.e., above 6 years old and under 15 years old) must attend a national primary school regularly.[340] The CE Act does not apply to children who are not SC, those who reside outside Singapore, or those beyond the compulsory school age.

For SC children residing in Singapore and born after 1 January 2012, their parents and/or caregivers must enrol their children in a national primary school, which refers to government/government-aided mainstream primary schools or government-funded special education (SPED) schools.

Full list of mainstream schools[341]

Full list of SPED schools[342]

GPP 5.1 ***Parents and caregivers should consult appropriate professionals when considering educational interventions and school placement for their child on the autism spectrum, such as clinical and educational psychologists who are informed on the special educational provisions in Singapore. [EM5-1]***

Children with severe complex conditions, including medical conditions or learning needs, may be unable to attend a national primary school (i.e., mainstream or government-funded SPED schools). These children need to be professionally assessed. Parents and/or caregivers can then apply, with supporting documents, to the Ministry of Education (MOE) for an exemption.[343]

In a small number of cases, some parents and/or caregivers may prefer to educate their children in alternative settings that are outside the national school system (e.g., home-schooling, full-time care or private education institutions [PEIs][343]). In such cases, professionals should advise these parents and/or caregivers on what would be beneficial for their children, taking into account the children's needs and educational interests, and refer them to MOE's website to apply for compulsory education exemption.[5] In their application, parents and/or caregivers would need to provide clear reasons why their child would be better supported in an alternative setting and propose suitably adequate education and/or care arrangements in lieu of attending a national primary school (i.e., mainstream primary or SPED school). Parents and/or caregivers also need to consent to regular monitoring processes, including the submission of education plans. For parents and/or caregivers enrolling their children into PEIs, they should also be aware that the PEI school fees are not subsidised by the government.

Information on exemption from compulsory education[343]

GPP 5.2 ***Professionals should be closely guided by Professional Practice Guidelines: Developmental and Psycho-educational Assessments and Provisions for Preschool-aged***

Children (2021) and Professional Practice Guidelines: Psycho-educational Assessment & Placements of Students with Special Educational Needs (2018) when advising parents on matters relating to education and transition. [EM5-1]

5.2 DEFERMENT FROM ENROLMENT INTO NATIONAL PRIMARY SCHOOLS

In some cases, parents and/or caregivers may consider deferring their child's entry into national primary schools. Decisions about a child's deferment into the national primary schools should only be made after careful evaluation of the child's needs and circumstances. Deferment could be considered for children who have been assessed to be able to access the mainstream curriculum but require additional time to develop the skills needed to access learning in a mainstream school setting. As this period of deferment is to allow the children the opportunity to level up their skills, professionals should recommend intervention during the period of deferment and review the children's progress and needs after intervention to more definitively ascertain placement.

For more details on deferment into national primary schools, please refer to the following:

Information on deferment from commencement of Primary 1 or Junior 1

5.3 CONSIDERATIONS WHEN DECIDING EDUCATIONAL INTERVENTIONS AND SCHOOL PLACEMENTS FOR CHILDREN ON THE AUTISM SPECTRUM AT PRESCHOOL AND SCHOOL AGE

GPP 5.3 ***When making recommendations for appropriate educational intervention and school placement, professionals should take into account (i) the developmental needs of individual children, their preferences, strengths and special interests, (ii) family contexts, and (iii) the range of support and services available for Early Intervention and School-age provisions for children with developmental and/or special educational needs. [EM5-2]***

Healthcare and educational professionals should adopt an individualised assessment approach, which takes into account a child's cognitive abilities, achievement skills, adaptive functioning, behavioural skills, and socio-emotional competencies, when determining an appropriate educational placement and planning educational supports needed by children on the autism spectrum across mainstream and SPED school settings.[4] For some children on the autism spectrum, the national curriculum and in-class support with minimal instructional modifications could be appropriate, whereas others may require significant curriculum customisation and instructional adaptations, which are offered in a SPED school setting.

GPP 5.4 ***Professionals should ensure that parents and/or caregivers are adequately supported to make informed decisions that can meet the longer-term educational needs, each***

child's preferences, strengths, and special interests, as well as the families' contexts. [EM5-2]

Information and recommendations provided by professionals to families are to be objective, evidence-based, and aligned to the child's educational interests, particularly when considering the child's longer-term educational needs. In situations where professional advice differs from parents or caregivers' preferences, professionals should respectfully acknowledge parents and/or caregivers' preferences without compromising on the integrity and objectivity of their professional judgment. Professionals must recognise that parents and/or caregivers may need time and support to navigate through this complex decision-making process. If needed, physicians in hospitals may refer parents and/or caregivers for further counselling with medical social workers.

These conversations with parents and/or caregivers should be positively framed to provide the confidence and knowledge for parents and/or caregivers to take on an active role as their child's co-educators and work closely with their child's teachers. Professionals providing advice to parents, caregivers, and teachers about school-based and educational support should have current knowledge and understanding about the wider landscape of Early Intervention (EI) and school-age provisions for children with developmental and/or special educational needs in Singapore. These professionals should refer to the following documents for more information:

Professional Practice Guidelines: Developmental and Psycho-educational Assessments and Provisions for Preschool-aged Children (2021)[5]

Professional Practice Guidelines: Psycho-educational Assessment & Placement of Students with Special Educational Needs (2018)[4]

GPP 5.5 ***Professionals should engage in information sharing across agencies, if necessary, to ensure common understanding and to coordinate support for the child. [EM5-2]***

5.3.1 Educational Interventions and School Placements at Preschool Ages – Birth to 7 Years Old

Children from birth to 7 years old who have been assessed with developmental needs, including children on the autism spectrum, can receive intervention through government-funded EI programmes.[344] Apart from EI programmes, children may also seek medical consultations and interim therapy at KKH Department of Child Development (KKH-DCD) clinics and NUH Child Development Unit (NUH-CDU) clinics, which are under the national Child Development Programme (CDP)[a] funded by the Ministry of Health (MOH).

Parents should be guided to make informed choices for EI programmes from a range of government-funded EI providers and private EI providers. Healthcare professionals can also direct parents to preschools that provide some support for children with developmental needs, including children on the autism spectrum. These preschools include preschools with Development Support-Learning Support

[a]For more information, please refer to: https://www.kkh.com.sg/patient-care/areas-of-care/childrens-services/Pages/child-development.aspx and http://www.nuh.com.sg/our-services/Specialties/Paediatrics/Pages/Developmental-and-Behavioural-Paediatrics.aspx.

(DS-LS) programme and Inclusive Support Programme (InSP) (see Table 1 below for referral processes and the *Parent's Guide for Young Children Who Need Early Intervention*[345] for more information).

When guiding parents and/or caregivers in decisions about choosing an appropriate EI programme and/or preschool, healthcare professionals can highlight key considerations[5] such as: the individual child's developmental needs across these five domains[345] – (1) Social and Emotional, (2) Physical and Motor, (3) Language and Communication, (4) Vision and Hearing, and (5) Cognition; the type and duration/intensity of EI support available; qualifications and experience of the team; quality of the programme; family involvement and engagement; child safety; location; and transport. Reference to culturally appropriate normative developmental milestones is important in ascertaining the severity of children's developmental needs. The different types of EI programmes available are listed in Table 5.1.

Table 5.1: Different types of EI programmes based on setting and level of EI support

Settings	**Levels of EI Support** See footnote[b] below for details on the different levels of EI Support	**Types of Government-Funded EI Programmes**[344] A brief description of these various EI Programmes is provided in Annex 5.1	**Referral Agency**
Preschool	Low	Development Support – Learning Support (DS-LS)	Child's Preschool
		Development Support Plus (DS-Plus)	EI professional at child's EIPIC centre
			Hospitals (KKH-DCD or NUH-CDU) or Private Paediatricians to SG Enable upon parental consent
	Low to Medium	Inclusive Support Programme (InSP)	
EI Centre	Medium to High	EIPIC Under-2s	
		EIPIC @ Centre	
		Enhanced Pilot for Private Intervention Providers (PPIP)	

Abbreviations: EI, early intervention; EIPIC, early intervention programme for infants and children; KKH-DCD, KKH Department of Child Development; NUH-CDU, NUH Child Development Unit.

For EI programmes which require referral from a paediatrician, parents may approach a physician at any polyclinic for a referral for assessment at the KKH-DCD or NUH-CDU, or approach a private paediatrician for assessment and recommendation. Once the child has been assessed suitable for a programme and parental/caregiver consent has been given, the hospital or private paediatrician will submit the online or hard copy application to SG Enable using the Social Service Net – Enabling

[b] *Low levels of EI support* are for short-term support (e.g., 6 months or less) and are delivered less frequently (e.g., once a week) for a short duration (e.g., one hour). These are typically delivered at the child's preschool (e.g., DS-LS, DS-Plus programme). *Medium levels of EI support* are for longer term support (e.g., one year or more) that is delivered more frequently (e.g., a few times a week) for longer durations (e.g., two or more hours) by a team of EI professionals and Allied Health Professionals (e.g., EIPIC). *High levels of EI support* are delivered on a one-to-one basis over an extended period of time.

Services (SSNet-ES) or via email or post. Upon receiving the referral, SG Enable will contact parents and/or caregivers to follow up with the application.

Professionals may refer parents to the following guide for more information about the various offerings and pathways for preschool-aged children.

Supporting Your Child – A Parent's Guide for Young Children Who Need Early Intervention[345]

5.3.2 Educational Interventions and School Placements at Formal School-ages – 7 Years Old and Above

Parents will need to make important decisions about school placements as part of the transition planning process from EI to school-aged provisions when the child approaches the compulsory school age[c]. Features for educational support for children on the autism spectrum in Singapore schools are discussed in more detail in the Section 5.4.

Key guidelines for professionals[5] when supporting parents with school-aged school placements decisions are that:

GPP 5.6 ***Parent and/or caregiver engagement with regard to educational placement should be an ongoing process that is initiated as timely as possible, typically initiated as the child approaches 5 years old and/or is in Kindergarten 1. [EM5-2]***

Some of the key questions when in discussion with parents and/or caregivers around choosing an appropriate school-aged provision for the child may include:

- What are the child's special educational needs?
- What kind of support does the child need to meet these needs?
- Where can this support be found - mainstream primary or SPED school?

GPP 5.7 ***Professionals should assist parents to obtain a Comprehensive Needs Assessment for Transition Support for their children on the autism spectrum who are approaching school-going ages. [EM5-2]***

These assessments are typically conducted by professionals in EI centres and/or hospitals[d]. Information is systematically collected from various sources such as feedback from parents, feedback from teachers, direct observations or assessments, medical records and past interventions (if any). Based on the information gathered, professionals make an initial assessment on the severity of the child's needs, and whether the child would need targeted, specialised provisions in the long term. This initial assessment should take into account the child's (i) level of cognitive functioning and (ii) level of adaptive functioning based on the various sources of information (e.g., parents/caregivers, school).

[c]Compulsory school age refers to the child being above 6 years old as of 1st January of the following year.

[d]More information can be found at https://www.moe.gov.sg/special-educational-needs/understand/assessment.

For children initially assessed to need specialised educational provisions (e.g., SPED), or for whom it is unclear if the child's severity of needs can be adequately supported in a mainstream primary school, it is crucial for professionals to follow up with a formal, comprehensive school readiness assessment that evaluates the support needed based on the child's needs. This comprehensive evaluation should include the use of standardised assessments to assess the child's school readiness in (1) cognitive functioning and (2) adaptive functioning skills.

Based on the information obtained from the comprehensive evaluation, professionals form a robust conclusion and make an independent and objective recommendation to parents/caregivers about the child's long-term educational placement. Notwithstanding this, the final decision regarding the choice of educational placement lies with the parent/caregiver. Professionals can refer to the *Professional Practice Guidelines (PPG) for Preschool-Aged Children*[5] for information on the commonly used standardised assessments to assess cognitive and adaptive functioning, and the assessment guidelines to ascertain children's suitability for mainstream or SPED schools.

Parents can be directed to the following MOE's guides for information on the types of support available in both mainstream and SPED schools, and the types of support that will meet the child's needs:

Which school for my child? A Guide for Parents of Children with Special Educational Needs[346]

How to choose a primary school[347]

MOE website on the various post-school pathways[348]

It should be noted that as the educational landscape evolves with time, the provisions and options available for students with special educational needs (SEN) will also change. Professionals may refer parents to the MOE website "*How to choose a primary school"*[347] for up-to-date information on the various available school-aged education offerings and pathways.

Parents who may wish to appeal for their children to be exempted from CE on the grounds of SEN must be advised by professionals to consult the MOE Compulsory Education Unit. Refer to Section 5.1.

5.3.2.1 SPED School Admission and Transfer processes

For more information on the process of admission and/or transfer to a SPED school, professionals may refer parents to the following MOE websites.

Apply to a special education school – For Singapore Citizen and Permanent Resident children applying to Primary 1 or Junior 1, and Returning Singaporeans applying to all levels[349]

Transfer to a special education school – For students currently in mainstream or specialised school[350]

Learn how and where to get an assessment done and when it is needed[351]

For preschoolers applying to Primary 1 or Junior 1, and returning Singaporeans applying to all levels and seeking admission into SPED school, healthcare professionals and/or psychologists at a government-funded hospital or private clinic should assist parents in the relevant sections of the SPED application form – Section 3 Medical report and Section 4 Psychological report. Private psychologists should be registered with the Singapore Register of Psychologists and have the relevant qualifications and experience before engaging the child for an assessment.

For students who are currently in a mainstream school or a specialised school (e.g., Northlight School and Assumption Pathway School), midstream transfers to SPED schools are centrally facilitated by MOE to ensure appropriate placement and a smooth transition to a SPED school setting. Professionals should direct parents to approach their child's current mainstream school's Principal for assistance on the transfer process to a SPED school. SPED schools will not accept direct applications from parents, legal guardians, private professionals, or hospitals.

Professionals are strongly encouraged to work closely with MOE to facilitate the transfer from mainstream schools to SPED schools. Healthcare professionals should not provide recommendations of SPED schools for educational placement, as MOE will facilitate school transfers. Healthcare professionals should also work closely with the student's current mainstream school to share information and discuss potential supports.

5.4 EDUCATIONAL SUPPORT FOR STUDENTS ON THE AUTISM SPECTRUM

For school-going students, the educational context in Singapore adopts a differentiated approach consisting of mainstream schools and SPED schools to cater to the wide-ranging needs of students with SEN, including students on the autism spectrum.

This section begins by providing some key practice guidelines that inform the general features of educational support for students on the autism spectrum. It then describes additional educational supports specific to mainstream and SPED schools in Singapore.

Undergirding all support for children and students with SEN is the need to engage parents and caregivers. Parents are key partners as they provide valuable insights into their child's unique needs. A collaborative partnership with the family and professionals can contribute to the effectiveness of

interventions, particularly when intervention strategies are generalised across multiple settings, such as the home, school and community.[352] Professionals may refer to Chapter 9 on Caregiver and Family Support for more detailed professional practice guidelines and recommendations when engaging with parents and/or caregivers.

5.4.1 General Features of Educational Support for Students on the Autism Spectrum

GPP 5.8 ***Educators teaching students on the autism spectrum should be provided with knowledge and skills to provide reasonable accommodations and supports for these students in their classrooms. The depth/scope of information and mode of training should be adapted/customised to their specific teaching and learning context. [EM5-3]***

The key features of educational support for students on the autism spectrum embraced by both school systems in Singapore include:

- Evidence-based teaching approaches for students on the autism spectrum
- Structured learning environments
- Tiered System of Support.

5.4.1.1 Evidence-based Teaching Approaches for Students on the Autism Spectrum

Research has shown that students on the autism spectrum demonstrate progress in the achievement of skills when instructional approaches used are both comprehensive and systematic.[353] Systematic instruction involves the provision of a structured teaching plan to ensure firstly, the maintenance and generalisation of learned skills, and secondly, high student engagement across classroom and school activities.[354]

Teaching approaches that have been found to be effective when teaching children on the autism spectrum include providing clear and succinct instructions on task requirements and behavioural expectations, using visual with verbal prompts to deliver instructions on task requirements, implementation of a prompting schedule of I-do (visual prompt), We-do (model prompt), and You-do (physical assistance), shortening of task requirements and employing frequent breaks to help pace task demands and regulate a student's emotions, and incorporating structured breaks like sensory and/or preferred activities in-between task activities.

5.4.1.2 Structured Learning Environments

Research literature suggests that students on the autism spectrum benefit from having structure within their learning environment. A structured environment allows a student on the autism spectrum to predict what is currently happening within the learning process and what will happen next, anticipate task requirements and the expected behaviours of specific learning settings, and learn and generalise a variety of skills to other learning contexts.

Key practice strategies that assist in structuring the learning environment include employing visual cues or supports that provide a schedule of activities for the day and for the current class period. This could be done visually via objects, pictures, and/or in written format, depending on the student's developmental abilities. Other strategies include organising the instructional setting to form a work area, as well as a quiet area, to help students perceive the salience of expected behaviours given the allocated environment setting; planning and providing choice-making opportunities; facilitating transitions and changes in daily routines and classroom schedules using visual schedules and timers to pre-empt sudden changes or routine transitions across activities and/or settings; and planning and providing systematic behavioural supports in terms of antecedent/preventive and/or consequence-based (i.e., individual reinforcement driven supports) strategies.

5.4.1.3 Tiered System of Support

The Tiered System of Support (TSS) is a framework that facilitates the systematic planning of support for students with SEN in Singapore's mainstream and SPED schools, so as to improve holistic

outcomes for all students. Under this framework, there are three tiers of support which are differentiated by the intensity of the support provided.[355,356] Support may be provided by teachers, specialised personnel (e.g., Learning Support Coordinators, Teachers trained in Special Needs, School Counsellors, Teacher Counsellors, SEN Officers) and professionals from external agencies.

Tier 1: Support for all students. Tier 1 supports include structured language and literacy instruction, and strategies that are beneficial for all students.

Tier 2: Additional support for some students. Tier 2 supports are provided in addition to Tier 1 supports. Tier 2 supports are offered to at-risk students with early targeted support through group-based interventions such as remedial lessons or social skills groups.

Tier 3: Intensive targeted support for a few students. Despite the availability of Tier 2 support, a few students with persistent difficulties may continue to require intensive and individualised intervention. As such, these students may require Tier 3 supports such as specific interventions, for example Circle of Friends (CoF).

5.4.2 Additional Educational Supports Available in Mainstream Schools in Singapore

GPP 5.9 ***School-based support provisions in mainstream schools should be based on the students' observed needs, and not solely on their diagnoses. [EM5-3]***

Students are provided with support based on their individual needs. In matching the student's needs to the type or intensity of support required, a Response to Intervention (RtI) approach is adopted by all mainstream schools. Using the TSS as a framework to guide support planning for students with SEN, students who are observed to require support beyond Tier 1 will be identified by the school for additional Tier 2 and Tier 3 support to improve holistic outcomes.[356]

GPP 5.10 ***School-based educational provisions offered to students on the autism spectrum should be determined by educational professionals working directly with the child, in consultation with parents, schools and when necessary, allied health professionals. [EM5-3]***

The school-based support available in all mainstream schools that could be applicable for students with SEN, including those on the autism spectrum, are literacy and numeracy support, Mother Tongue language acquisition, social-emotional wellbeing, sexuality education, education and career guidance, and access arrangements for examinations.

5.4.2.1 Literacy Support

Students on the autism spectrum who also have literacy difficulties or have been diagnosed with dyslexia may access programmes supporting literacy development available through mainstream schools.

Students who lack early literacy skills will be identified upon entry at Primary 1 to join the Learning Support Programme (LSP). The LSP focuses on building foundational English language skills so that students can access learning in a regular classroom. LSP lessons are conducted by teachers who have received additional training in delivering LSP,[357] and who are known as Learning Support Coordinators.

At Primary 3 and 4, students with reading difficulties may be supported in the Reading Remediation Programme (RRP). Those with significant literacy difficulties and dyslexia may be emplaced in MOE's 2-year School-based Dyslexia Remediation (SDR) programme. Both these programmes are conducted by teachers who have received additional training.

Students who require continued support for dyslexia after Primary 4 may enrol in the MOE-subsidised Main Literacy Programme at the Dyslexia Association of Singapore (DAS)[e]. This programme supports students up to the secondary school level.[358] Some students may also find the curriculum differentiation in Foundation Subjects at Primary 5 and 6 more suitable, and these classes are typically smaller in size.

5.4.2.2 Numeracy Support

Students who need additional support in acquiring basic numeracy skills are identified upon entry at Primary 1 to join the Learning Support for Mathematics (LSM) Programme. This support is provided to students on a needs basis until Primary 4[f]. At Primary 5 and 6, the option of Foundation Mathematics is available to students who continue to face significant numeracy difficulties.

Beyond the LSM programme, low progress learners in mathematics at primary and secondary levels are supported by teachers trained in appropriate pedagogies through the Improving Confidence and Achievement in Numeracy (ICAN) effort.

5.4.2.3 Support for Mother Tongue Language Acquisition

Bilingualism is a cornerstone of Singapore's education system. Students are encouraged to learn Mother Tongue Language (MTL) to as high a level and for as long as possible.[359]

Differentiated curriculum is offered from primary to pre-university levels. Students with difficulties coping with the standard MTL curriculum may consider offering MTL at a lower level.[4] Primary 3 and 4 students who require a stronger foundation in oracy and literacy skills may be supported through the Mother Tongue Support Programme (MTSP). MTSP is conducted in small classes by trained school teachers. After Primary 4, students with persistent difficulties in coping with the standard MTL curriculum could be offered the Foundation MTL curriculum at Primary 5 and 6, and the MTL 'B' curriculum at Secondary and Junior College levels, which focus on the development of oral and listening skills, with a reduced demand on writing skills.

Students with certified SEN that severely affects their ability to cope with overall learning may be recommended by the school for exemption from a component of the MTL subject (e.g., oral examination, listening comprehension) or exemption from offering MTL (including at the national examinations). In evaluating applications for MTL exemption, MOE takes into account not only the diagnosed SEN, but also how students are coping across different subjects in school (i.e., beyond MTL).

5.4.2.4 Support for Social Emotional Learning (SEL)

Social-emotional competencies are taught and learnt through the Character and Citizenship Education (CCE) curriculum,[360] within the broader context of values learning and application. SEL is taught in a caring, supportive and safe school environment, where authentic learning opportunities through student development experiences, such as school camps and co-curricular activities, allow students to also practise and internalise these competencies. Depending on their needs, students who require more support in terms of mental health, social or family needs may receive support from specialised school personnel such as Teacher-Counsellors, School Counsellors or Student Welfare Officers.[361] School counsellors provide support to students with social, emotional, behavioural, and mental health issues, while Student Welfare Officers work with students with irregular attendance or are involved in statutory cases. Students who are identified to require more intensive intervention may be further referred to community-based professionals, such as the multi-disciplinary Response, Early intervention, Assessment in Community mental Health (REACH) or social service agencies.

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[e]Information about the programme, the referral process as well as the locations of DAS centres can be found here: https://das.org.sg/services/programmes/main-literacy-programme.html

[f]Primary 4 LSM will be rolled out in 2024.

Primary 1 students identified with social and behavioural difficulties may also receive support under TRANsition Support for InTegration (TRANSIT). TRANSIT aims to ease the students' transition into primary school by helping them develop foundational self-management skills.[362] The support in TRANSIT will focus on strengthening self-management skills, with students learning good classroom work habits, regulating their emotions well and developing their social and communication skills.[363] Students learn these skills through (a) a direct-teaching approach involving role-play, independent practice and coaching by trained staff, followed by (b) infused practising of these learnt skills in everyday classroom and school settings. Generalisation at home settings is also crucial, with parents roped in to reinforce practising of learnt skills with their children. Key school personnel, form and subject teachers, and SEN Officers forming the School TRANSIT Teams, undergo training to equip them with skills and knowledge to identify students suitable for the TRANSIT intervention. The School TRANSIT Teams provide support for students in TRANSIT, as well as work with teachers to enhance classroom practices to build supportive systems for social and behavioural needs.

Primary and Secondary students who may require social or emotional support and would benefit from peer support to overcome their specific areas of difficulties may also be selected for school-based intervention programmes such as the CoF and Facing Your Fears (FYF) for secondary schools. See Annex 5B and 5C for more information about the intervention programmes.

5.4.2.5 Support for Sexuality Education

Sexuality Education in mainstream schools is delivered through the formal curriculum through Science lessons, and the CCE curriculum.[364] At lower primary, through lessons on safety and safeguarding, students learn to protect themselves from sexual abuse in real life and online, their right to safety, as well as how to seek help from trusted adults. The upper primary and lower secondary Science and upper secondary and JC/CI Biology syllabi cover the topics of sexual reproduction in humans, sexually-transmitted infections (STIs), and medical advancements in human reproduction.

Sexuality Education lessons for Primary 5 to JC/CI students comprise classroom lessons covering topics such as building healthy and respectful relationships, dating and marriage, consequences of teenage sexual activity and pregnancy, influence of the online media on sexuality, and safety and protection from sexual abuse and grooming. Empowered Teens (eTeens) is an STIs/HIV prevention programme developed by Health Promotion Board (HPB) in collaboration with MOE for Secondary 3 and JC/CI 1 students and delivered through mass talks. There is also a classroom-based lesson for Secondary 3 students.

In addition to the delivery of Sexuality Education through the formal curriculum, schools adopt a tiered approach, with different levels of prevention and intervention efforts and personnel involvement, for students who are facing sexuality-related issues and require further support.

5.4.2.6 Support for Education and Career Guidance

Through the incorporation of Education and Career Guidance (ECG) lessons and Student Development Experiences in primary to post-secondary school levels, and the MySkillsFuture Student Portal, ECG helps students develop a sense of purpose in life. By nurturing self-awareness and self-directedness for lifelong learning, students develop a growth mindset, adaptability and a resilient attitude to embrace future opportunities and appreciate the value of all occupations.[365] In addition, Secondary Schools, Junior Colleges/Millennia Institute and Post-Secondary Education Institutions (PSEIs) are resourced with ECG Counsellors to guide students in making informed decisions.[365] Secondary and Junior College/Millennia Institute students with additional needs may receive further guidance and support from teachers and other school personnel such as SEN Officers. The ECG Centre@MOE also provides ECG counselling services for students during periods such as the release of their GCE N-Level, O-Level and A-Level examination results. At PSEIs, including ITE, polytechnics, and universities, Support Officers prepare students with SEN for employment by partnering the community and industry to identify internship opportunities and provide pre-internship and employment workshops.[366]

5.4.2.7 *Access Arrangements*

Access Arrangements (AA) are examination arrangements granted to students with specific needs so that they may sit for the national examinations with reduced barriers arising from their SEN without compromising the assessment objectives or standards being tested.[367] AA must not grant the student an unfair advantage over other students.[4]

Recommendations for AA should be based on the student's specific needs and the student's familiarity with the specific arrangements, and not solely on the student's disability or diagnoses. The recommendations should be accompanied by clear and current evidence of functional needs to demonstrate that the recommended arrangements would be appropriate, which can be provided by the school or professionals who work directly with the student. The student's needs should also be reviewed periodically.

5.4.3 Additional Educational Supports Available in SPED Schools in Singapore

SPED schools in Singapore cater to students with moderate-to-severe SEN who require more intensive and specialised support to meet their educational needs. These schools are equipped with specialised manpower and customised facilities, and offer customised curricula and programmes.

GPP 5.11 ***Parents and caregivers should be referred to the MOE website for an up-to-date list of SPED schools that support students on the autism spectrum. [EM5-3]***

The range of SPED schools available includes schools that cater to students on the autism spectrum, with no intellectual impairment, and who can access the national curriculum, as well as schools that cater to students on the autism spectrum, with intellectual impairment, and may require a customised SPED curriculum (see QR code on p.95).

5.4.3.1 *Specialised Manpower and Customised Facilities*

GPP 5.12 ***Educational support for students on the autism spectrum with moderate-to-severe special educational needs in SPED schools should involve a multi-disciplinary team of specially trained teachers and Allied Health Professionals, as well as customised facilities to support teaching and learning. [EM5-3]***

SPED teachers receive specialised training on evidence-based pedagogies to teach and support students with moderate-severe SEN. Low teacher-student ratios allow for more individualised instruction and support, especially for students with higher social-emotional and behavioural needs.

In addition, students in SPED schools have access to specialised support from Allied Health Professionals, such as psychologists, speech and language therapists, occupational therapists, and physiotherapists. Social workers may also assist families with family life support services such as counselling, financial assessments, and caregiver and sibling support.

SPED schools are equipped with customised facilities to better support teaching and learning for a range of disability profiles, such as sensory and therapy rooms, hydrotherapy pools, and dedicated rooms to teach Daily Living Skills and Vocational Education.

5.4.3.2 *Customised Curriculum Approach*

GPP 5.13 ***Specialised and individualised curriculum, guided by MOE's SPED Curriculum Framework, should be provided in accordance to each student's needs and ability. [EM5-3]***

SPED schools are guided by MOE's SPED Curriculum Framework[368] in developing a holistic, customised curriculum for their diverse student profiles. The framework specifies the key learning domains for holistic SPED, namely, i) Communication and Language, ii) Numeracy, iii) Social-Emotional Learning, iv) Daily Living Skills, v) Arts, vi) Physical Education, and vii) Vocational Education. The

framework further emphasises Information and Communications Technology as an enabler for teaching and learning, and CCE as the foundation for values-based SPED.

Teaching and learning are highly individualised through an Individual Education Plan (IEP) in the primary/junior years and an Individual Transition Plan (ITP) in the secondary/senior years for every SPED student. IEPs and ITPs help focus instructional planning and support on the priority goals of the student from the point of entry to school to the point of graduation to ensure successful transition to post-school outcomes. These plans also contain each student's personalised goals which are closely monitored by teachers to facilitate their access to the curriculum and success in the home and community.

5.4.3.3 Support for Communication and Language

SPED students develop receptive and expressive communication and language skills[g] through the areas of prelinguistic communication: Listening, Speaking, Reading and Writing. With functional grammar, vocabulary and pragmatics taught alongside language skills, students will learn to comprehend and use language appropriately, communicate meaningfully and purposefully during interactions, and use appropriate modes of communication across a wide range of situations. Students with higher level of needs can have access to visual supports and multi-modal teaching resources used by teachers, interventions by speech and language therapists, and appropriate assistive technology (e.g., Alternative and Augmentative Communication devices) to support effective communication.

5.4.3.4 Support for Daily Living Skills

The Daily Living Skills (DLS) learning domain equips SPED students with functional skills that will enable them to care for themselves and their well-being, and empower them to participate and exercise greater independence at home, in the community and in productive activities. There are five key areas in DLS, namely Self-Care, Health, Leisure, Home Living, and Community and Mobility. DLS is taught in SPED schools through evidence-based pedagogical practices, such as systematic instruction, explicit instruction and visual strategies including schedules and video-based instruction.

5.4.3.5 Support for Social Emotional Learning (SEL)

Through SEL, students develop knowledge, skills, and attributes in five core competencies of Self-Awareness, Self-Management, Social Awareness, Relationship Management, and Responsible Decision-Making. They learn to understand and manage themselves, as well as their relationships with others. They also learn to make informed decisions and solutions that consider the consequences to others and themselves. SEL is taught within a positive and collaborative school culture through pedagogical practices that are customised to students' needs, such as the use of explicit and systematic instruction, social stories, and social scripts.

5.4.3.6 Support for Sexuality Education

Sexuality Education in SPED schools is taught through the Healthy and Safe Relationships (HSR) programme, which covers three broad themes of body awareness, personal safety, and positive relationships. HSR develops students' understanding about the physiological, social, and emotional changes experienced while growing up, develops their social, emotional, and personal safety skills, and builds students' positive attitudes and beliefs towards themselves and their relationships with others. HSR is carried out through customised lessons according to the varying needs of students, with a range of teaching methods such as direct instruction, use of social stories, and role-playing.

[g]Receptive communication and language skills comprise of listening, reading and viewing, while expressive communication and language skills comprise of speaking, writing and representing.

5.4.3.7 Support for Vocational Education

Vocational Education in SPED is introduced at the secondary level and is taught through three content areas of Vocational Guidance, Soft Skills and Hard Skills. Vocational Education introduces students to the world of work, develops students' self-awareness of their interests, preferences, and strengths, and equips them with key competencies to be ready for valued contribution and to stay relevant. Vocational Education is taught collaboratively by a team of diverse professionals in SPED schools, including teachers, trainers and Job Coaches, with support from Allied Health Professionals.

5.4.3.8 Access Arrangements (AA)

Recommendations for AA can be made for students accessing the national curriculum in SPED schools too (see Section 5.4.2.7).

5.5 TRANSITION

Transitions into, out of, and between educational settings are often difficult for children on the autism spectrum because they are accompanied by unpredictability, which may cause confusion and anxiety for the child.[369] Key periods of transition occur (i) from diagnosis to intervention, (ii) from preschool or EI settings to formal schooling, (iii) within and across formal schooling settings, and (iv) from formal schooling to post-school pathways.

The following good practice principles may be generally applicable across various transition periods and individual support needs.

GPP 5.14 ***Professionals should ensure that transition support is systematically planned, holistic and person-centric; this includes having transition support differentiated based on the students' identified needs. [EM5-4]***

Transition support is best viewed as a long-term process designed around the learning, behavioural, socio-emotional, and physical needs of the student, rather than a singular event. Advance preparation and planning minimise stress, promotes wellbeing, and maximises the likelihood of a successful start in the next environment. As students on the autism spectrum may take time and practice to demonstrate independent and fluent adaptive skills, target setting in the current school-setting may be prioritized, so as to facilitate future transitions.

GPP 5.15 ***Professionals should encourage and empower parents and caregivers to plan ahead and support their child to reduce the impacts of transitions; this includes advocating for the child, sharing information, and working closely with receiving schools. [EM5-4]***

With parental and caregiver consent, healthcare professionals can help parents and caregivers to share information with receiving schools on their behalf. Alternatively, professionals can provide the information to parents and caregivers, who can then share it with the receiving schools or organisations.

The following sections describe key practice guidelines applicable to specific periods of transition.

5.5.1 Diagnosis to Intervention

Following a diagnosis, parents and caregivers may experience a range of emotions as they try to understand their child's SEN. These could include anxiety, grief, anger, fear, guilt, surprise, acceptance, and hope.

GPP 5.16 ***Professionals should provide families information about relevant support groups and organisations and recommended sources of information, as needed (i.e., taking into consideration family members' needs and contexts). [EM5-5]***

For parents and caregivers with children seeking EI services, SG Enable runs Step One training to provide parents and caregivers information on early intervention, techniques to engage their child, and available community resources and support.

Informal Support Groups[370]

Children Health Services

KK Women's and Children's Hospital[h]

National University Hospital[i]

Child Guidance Clinic[j]

Community-based Agencies

Family Service Centres:
Community-based resource centres offering a broad range of community services for families in need

[h]KK Women's and Children's Hospital: https://www.kkh.com.sg/patient-care/areas-of-care/childrens-services/Pages/child-development.aspx
[i]National University Hospital: https://www.nuh.com.sg/our-services/Specialties/Paediatrics/Pages/Developmental-and-Behavioural-Paediatrics.aspx
[j]Institute of Mental Health – Child Guidance Clinic: https://www.imh.com.sg/Clinical-Services/Outpatient-Clinics/Pages/Child-Guidance-Clinic.aspx

SG Enable

Home Page[k]

Social Service Agencies (SSAs)

Early Intervention Programme for Infants & Children (EIPIC) Centres:
Provides developmental and therapy services for infants and young children at risk of moderate to severe developmental delays

SHINE Children and Youth Services:
Provides social work and educational psychology services to children, youth, and their families

Autism-specific SSAs[l]
AWWA Ltd, Autism Resources Centre (Singapore), Autism Association (Singapore), Rainbow Centre and St. Andrew's Autism Centre

For further information on SSAs and other organisations

5.5.2 Transition from Preschool/Early Intervention to Formal Schooling Settings

The transition from preschool or EI settings to formal schooling settings (e.g., mainstream primary school or SPED schools) imposes demands on children's communication, social, emotional, and adaptive skills, which are areas of difficulties for children on the autism spectrum.[371]

GPP 5.17 ***When transitioning from preschool to formal schooling, children on the autism spectrum may benefit from explicit teaching and/or reinforced practices in the home and community in skills such as functional communication, emotional regulation, behavioural regulation, social, and adaptive skills. [EM5-6]***

Most preschool and EI programmes have a school readiness programme before the end of K2, which would include teaching of skills needed to prepare for formal schooling.[372]

Self-care and organisation skills. These include self-care skills such as going to the toilet, wearing one's uniform, as well as organisation skills such as taking care of one's belongings, packing one's school bag according to the timetable, and writing down important information for the next school period or day.

[k]SG Enable – Your First Stop for Disability and Inclusion in Singapore: https://www.sgenable.sg/Pages/Home.aspx
[l]Ministry of Education: https://www.moe.gov.sg/special-educational-needs/understand/support.

Familiarisation with routines. Children on the autism spectrum benefit from the practicing of routines, such as the following of personalised school timetables, as well as the familiarisation of rules and expected behaviours. Having a healthy sleep and eating routine is equally important to ensure that they are ready to engage in school activities.[372]

Social and communication skills. These are a prerequisite for activities in both mainstream primary and SPED schools. These skills may be taught and practised through modelling or role-play. Professionals can encourage parents to create opportunities for practicing social and communication skills,[372] such as expressing their needs and wants, asking for help, initiating, and having conversations, turn-taking, and sharing one's belongings with others.

Emotional regulation skills. These involve the ability to manage and respond to an emotional experience and are important for navigating situations in school. Children on the autism spectrum may have difficulties regulating their emotions and may be taught skills to handle the variety of emotions faced as part of the formal schooling experience. Teaching children on the autism spectrum to identify the emotions they feel, as well as to use relaxation techniques, such as deep breathing or progressive muscle relaxation, would help to prepare them for school.

Healthcare or educational professionals should have discussions with parents and/or caregivers on how they can reinforce the skills taught at home and in the community. Professionals may direct parents to the following resources to help with school transitions:

"Preparing Your Child For A New School - A Resource Kit for Parents of Children with Additional Needs"[372]

"Parent Kit – Starting Your Primary 1 Journey"[373]

5.5.3 Transition within and across Formal Schooling Settings

Within the mainstream or SPED primary schools, students on the autism spectrum will transition across levels and experience changes in teachers, peers, and academic demands. Students may also transition between school settings (e.g., from a mainstream or specialised school to SPED school and vice versa, between SPED schools, from a mainstream primary to a mainstream secondary school, from a primary school to another primary school). These transitions require students to adjust to different settings and curriculum structures (e.g., class sizes, longer school hours, new subjects, greater demand to be independent and self-disciplined) while managing personal changes across their development.[374]

Appropriate transition support is important to help students manage the changes that they will experience as they move to a new level or school. The TSS framework guides mainstream and SPED schools in planning for transition support across schools. Differentiated support, designed based on students' needs, is provided to all students with SEN, including those on the autism spectrum.

Tier 1: Support for all students. There are school- and level-wide processes for transition support to help all students make a positive transition to the next schooling setting. Receiving schools will collate and review information about incoming students. Transition support activities such as orientations, induction programmes, or workshops for students and parents will typically be organised by schools to provide students and parents the knowledge about the new environment, build necessary skills, and foster a positive attitude towards the impending transition.

Tier 2: Additional support for some students. Some students with mild to moderate SEN in the area of learning, behaviour, and/or social-emotional wellbeing may require additional transition support in addition to the Tier 1 provision for all students. If needed, a transition support planning meeting involving the student, family, and sending and receiving schools could be arranged to discuss support plans.

Tier 3: Intensive and targeted support for a few students. Students with moderate to high SEN in the areas of learning, behaviour and/or social-emotional wellbeing may require added intensive transition support that is customised to their needs. Intensive and targeted transition support may entail planning for specific goals and support which target the student's needs, providing a longer runway to implement support, involvement of more stakeholders (e.g., family, Allied Health Professionals, external agencies), more thorough and frequent communication to discuss and coordinate individual transition support plans, and closer monitoring of student's coping during the transition period.

GPP 5.18 ***Professionals working with students on the autism spectrum who are transitioning within and across formal schooling settings (i.e., mainstream schools, specialised schools and SPED schools) should work alongside schools and parents to support the timely and accurate dissemination of relevant information with receiving school personnel. [EM5-7]***

Both sending and receiving schools have a responsibility to ensure that there is sufficient information about the student in order for effective transition support to take place. Healthcare professionals, with parental or caregiver consent, may be required to provide an updated assessment of the child's needs.

5.5.4 Transition from Formal Schooling to Post-school Pathways

The ultimate goal of education is to prepare children, including those on the autism spectrum, to be contributing and valued members of society, and to lead a life of independence, leisure pursuits, continual learning, participation in the community, and employment. The transition from formal schooling to post-school options and eventually integration into society is hence an important part of a student's educational journey.

5.5.4.1 Key stages of Transition Planning

Careful planning and coordination between stakeholders is critical for successful post school outcomes.[375] SEN Officers in mainstream secondary schools and Transition Planning Coordinators (TPC) in SPED schools provide support to students with SEN during the transition to post-school pathways.

SPED schools work with students and their parents to provide support through a structured transition planning process that begins when the student enters the secondary years. At every transition planning stage, students' interests, preferences, employability and strengths are considered.

Transition Planning takes place through three key stages. In the early secondary years (13–14 years old), families are first introduced to the importance of future planning for their child's successful transition to post-school pathways. Families are encouraged to learn about their child's interests, preferences, and strengths to better plan for suitable post-school pathways. Information about post-school pathways, services and schemes available to support their child for adult living are shared with families.

In the middle secondary years, starting at around 15 years of age, families participate in envisioning and collaborative planning meetings to explore their child's interests and aspirations, and develop an Individual Transition Plan (ITP). The ITP captures each child's personalised post-school goals, and outlines the supports and strategies needed to help them achieve their aspirations and dreams. The ITP also guides teachers in customising teaching and supports for students and is reviewed yearly to ensure that students' progress and post-school goals are updated and refreshed.

In the final schooling years (i.e., 17–18 years old), SPED schools initiate activities to match and link families with suitable post-school agencies. Students' ITPs are consolidated and used to facilitate the transition.

5.5.4.2 Range of post-school pathways and options

GPP 5.19 ***When transitioning to post-school pathways, students on the autism spectrum and their parents and/or caregivers should be provided information about the range of post-school options and the pre-employment and/or employment support. [EM5-8]***

Students with SEN, including students on the autism spectrum, who graduate from mainstream secondary schools and SPED schools may apply to (i) specialised vocational training schools for further studies or vocational training; (ii) or Institutes of Higher Learning (IHL) (i.e., Institute of Technical Education (ITE), polytechnics, Autonomous Universities and Arts Institutions). Other post-school options include sheltered workshops and day activity centres.

Professionals may refer parents to the following resources:

MOE website on the various post-school pathways[348]

SG Enable website on the various training and employment opportunities[376]

MOE Parent Kits on Post-Secondary Transition for students navigating the mainstream curriculum[377]

Training opportunities offered by Enabling Academy[378]

Vocational Education. Students who are work-capable may progress to certificate programmes at Delta Senior School or Metta School from the age of 16 years. These eventually lead to nationally accredited Workforce Skills Qualification (WSQ) and national ITE Certificate (NITEC), which are the same as those awarded to students from the mainstream schools. Professionals may refer parents to Delta Senior School or Metta School for enquiries regarding programme prerequisites[m].

Alternatively, students who are work-capable may also participate in the School-to-Work (S2W) Transition Programme at 18 years old. The S2W Transition Programme is a structured programme by MOE, MSF and SG Enable, offered in all SPED schools. S2W aims to match students to an appropriate employment or provide further customised job training and support to prepare students for eventual

[m]Two SPED schools, Metta School and Delta Senior School, offer nationally accredited vocational certification programmes from the age of 16 up to 21, leading to ITE Skills Certification and/or WSQ certification.

employment[n]. These initiatives include internships in workplaces under the supervision of job coaches to gain real-world work experience. Referral of suitable applicants into the S2W Transition Programme is made by SPED schools. The S2W Transition Programme begins in the student's final year of school and extends up to two years after graduation.[376] Professionals may refer parents to the SG Enable website[o] for further information.

Information on S2W Transition Programme

Other post-school options for students with on the autism spectrum include work activities in a sheltered employment agency run by an SSA and social and recreational day programmes in a Day Activity Centre. SSAs also offer a range of other community services. SSAs and organizations that support people on the autism spectrum include AWWA Ltd, Autism Resources Centre (Singapore), Autism Association (Singapore), Rainbow Centre and St. Andrew's Autism Centre (see QR code on p.99).

Institutes of Higher Learning (IHL). Each IHL has a dedicated SEN Support Office (SSO) or SEN coordinators on campus that coordinates support for students with SEN, including those with autism from pre-enrolment to graduation.[379] The SSOs or SEN coordinators engage students to understand their individual needs, and work with lecturers and tutors to provide in-class learning assistance and access arrangements. Pre-internship workshops covering topics such as workplace norms and communication skills are also conducted to help students cope with the transition to work. The SSOs or SEN coordinators also collaborate with community and industry partners to run mentorship programmes, internship placements and job matching programmes.

The IHLs have funds that students with SEN can tap on to purchase education-related assistive technology devices and support services, so that students can have equal access to their institutions' programmes and services. Students with SEN, including those on the autism spectrum, may approach the SSO, SEN coordinators or SG Enable directly to obtain support for work preparation. SG Enable's IHL-to-Work programme is complimentary for SC and Permanent Residents only.

Information on IHL-to-Work Programme offered by SG Enable[380]

Abbreviations

AA, Access Arrangements; ASD, autism spectrum disorder; CCE, Character and Citizenship Education; CDP, Child Development Programme; CE, compulsory education; CoF, Circle of Friends; DAS,

[n]The School-to-Work Transition Programme is a national programme by MOE, MSF and SG Enable, offered in all SPED schools, to support students with more diverse profiles to transit to possible employment.

[o]SG Enable – School-To-Work (S2W) Transition Programme: https://www.enablingguide.sg/im-looking-for-disability-support/training-employment/school-to-work-(s2w)-transition-programme

Dyslexia Association of Singapore; DLS, Daily Living Skills; DS-LS, Development Support-Learning Support; ECG, Education and Career Guidance; EI, early intervention; EIPIC, Early Intervention Programme for Infants & Children; FYF, Facing Your Fears; HPB, Health Promotion Board; HSR, healthy and safe relationships; IEP, Individual Education Plan; IHL, Institutes of Higher Learning; InSP, Inclusive Support Programme; ITE, Institute of Technical Education; ITP, Individual Transition Plan; KKH-DCD, KKH Department of Child Development; LSM, Learning Support for Mathematics; LSP, Learning Support Programme; MOE, Ministry of Education; MOH, Ministry of Health; MTL, mother tongue language; MTSP, Mother Tongue Support Programme; NITEC, national ITE Certificate; NUH-CDU, NUH Child Development Unit; PEI, private education institution; PPG, professional practice guidelines; PSEIs, Post-Secondary Education Institutions; REACH, Response, Early intervention, Assessment in Community mental Health; RRP, Reading Remediation Programme; RtI, Response to Intervention; S2W, School-to-Work; SC, Singapore citizens; SDR, School-based Dyslexia Remediation; SEL, Social Emotional Learning; SEN, special educational needs; SPED, special education; SSAs, Social Service Agencies; SSO, SEN Support Office; STIs, sexually-transmitted infections; SSNet-ES, Social Service Net – Enabling Services; TPC, Transition Planning Coordinators; TRANSIT, TRANsition Support for InTegration; TSS, tiered system of support; WSQ, Workforce Skills Qualification.

ANNEX 5A – A BRIEF DESCRIPTION OF THE VARIOUS EI PROGRAMMES

1. The **Development Support – Learning Support (DS-LS)**[38] programme aims to provide short-term support for children who require low levels of EI support within their natural environment, i.e., the preschool setting. Children on the DS-LS programme receive EI within a preschool-setting at an intensity of about 1–2 hours per week on average.
   Referral to the DS-LS programme can be made through the child's preschool. Paediatricians who have assessed the child to require low levels of EI support can refer parents to contact the child's preschool. If the child's preschool currently does not offer DS-LS, preschools may contact the SG Enable Therapy Teams[p].

2. **Development Support Plus (DS-Plus) Programme**[q] targets children aged 2 to 6 years old who have made sufficient progress under the EIPIC@Centre programme and have generally progressed to require low levels of EI support. DS-Plus aims to support children in the transition to a mainstream classroom. Under DS-Plus, EI professionals from the EI centre will work with the child in his/her preschool up to twice a week, co-teaching the child alongside the preschool teacher. The intensity of EI support under the DS-Plus programme for children with low levels of EI support is about 2–4 hours per week on average.

   Admission into the DS-Plus Programme is conducted by the EI professional working with the child using the Early Intervention Benchmarking Framework[r]. If the child is suitable, the EI centre will first obtain parents' consent, before contacting the child's preschool principal to share more about the programme and to seek the preschool's agreement for the EI professional to support the child within his/her existing preschool.

3. The **Inclusive Support Programme (InSP) Pilot**[381] is a new programme piloted at selected preschools from October 2021. It aims to integrate both early childhood education and EI in a preschool setting for children with developmental needs aged three to six, who require medium levels of EI support. A preschool with InSP will be resourced with EI professionals and visiting Allied Health Professionals (i.e., therapists and psychologists) who will provide specialist support within the preschool, similar to that provided in EIPIC centres. For pilot preschools, the preschool environment will also be enhanced with rehabilitative and assistive equipment. With this support in place, a child who requires medium levels of EI support need not travel between the preschool and the EI centre.

4. **Early Intervention Programme for Infants & Children (EIPIC) Under-2s and EIPIC@ Centre**[382] programmes aim to support children who require medium to high levels of EI support. These programmes are delivered at EI centres by a team of EI Professionals and Allied Health Professionals.

   a. **EIPIC Under-2s** is targeted at children under 2 years old with an emphasis on upskilling parents and caregivers. Parents and/or caregivers are required to accompany the child, as the programme focuses on training the parent/caregiver to carry out intervention strategies

[p]SG Enable – Enabling guide: Information on how preschools can come onboard to offer DS-LS: https://www.enablingguide.sg/docs/default-source/default-document-library/information-on-how-preschools-can-come-onboard-to-offer-ds-ls.pdf
[q]For more information, please refer to http://www.nuh.com.sg/our-services/Specialties/Paediatrics/Pages/Developmental-and-Behavioural-Paediatrics.aspx and https://www.kkh.com.sg/patient-care/areas-of-care/childrens-services/Pages/child-development.aspx
[r]Enabling Guide by SG Enable. (n.d.). Annexes and Supplementary FAQs. https://www.enablingguide.sg/docs/default-source/default-document-library/annexes-and-supplementary-faqs.pdf?sfvrsn=81367e84_2

into the child's daily routines in their home setting. At the age of two, the child will transit into the EIPIC@Centre programme.

b. **EIPIC@Centre** programme provides intensive and customised support, including both therapy and educational intervention services, typically in small groups. There is a transdisciplinary team of EI professionals supporting the child's developmental needs, such as EI teachers, therapists, psychologists, and social workers. The intensity of EI support would typically be about 5–12 hours per week on average.

   Details on EI centres can be found on the SG Enable website: https://www.enablingguide.sg/im-looking-for-disability-support/therapy-intervention/early-intervention-programme-for-infants-children.

5. The **Enhanced Pilot for Private Intervention Providers (PPIP)**[383] programme is provided by Early Childhood Development Agency-appointed private EI centres. It offers more choices of EI for children who have been referred for the EIPIC. Children enrolled in the PPIP programme will receive subsidies that will help to partially defray the cost of the EI services received.

   Details on PPIP centres can be found at: https://www.enablingguide.sg/im-looking-for-disability-support/therapy-intervention/enhanced-pilot-for-private-intervention-providers

ANNEX 5B – CIRCLE OF FRIENDS

The Circle of Friends (CoF) is a school-based structured peer support intervention for students with social, emotional and behavioural difficulties. Students with SEN under CoF meet weekly with their Form Teacher or Special Educational Needs Officer (SEN Officer) and CoF peers, to identify their specific difficulties and devise strategies to address them.

CoF is conducted over five to eight sessions with the support of six to eight friends who have volunteered to be in the Circle. CoF has been offered to schools over the past few years on a request basis, with an MOE psychologist providing on-the-job coaching for the SEN Officer or the Form Teacher facilitating the Circle.

CoF peers are identified by school personnel (e.g., Form Teacher) who are familiar with the student with SEN and his/her peers. Peers selected are usually schoolmates whom the student with SEN is comfortable with, are mature, helpful, and keen to be part of the Circle.

At the start of CoF, the school personnel facilitate the first few sessions to set ground rules and provide basic knowledge of the CoF process and the challenges that a student with SEN faces. Through the subsequent CoF sessions, peers will be able to acquire deeper understanding of how best to support their friend and hone soft skills such as active listening and problem solving. The facilitator plays an important role in guiding the Circle to come up with practical solutions collectively and helping to ensure that discussions and responses (which can often be emotional) are addressed tactfully and constructively.

ANNEX 5C – FACING YOUR FEARS

The Facing Your Fears (FYF) is a school-based intervention to help students with SEN who struggle with emerging anxiety[s]. It consists of 10 weekly sessions after school, with a group of two to four students with SEN who meet with a facilitator who helps them become more aware of their anxiety triggers and symptoms. They learn self-management strategies such as thinking helpful thoughts, deep breathing and taking concrete steps to face their specific fears through incremental exposure.

The group setting allows the students with SEN to offer mutual support and encouragement to apply the self-management strategies during the sessions and beyond. FYF is conducted by SEN Officers who are trained by MOE Psychologists and Specialists.

[s]Students with more severe anxiety issues or mental health conditions would be referred to professionals such as REACH from the Institute of Mental Health (IMH). REACH stands for Response, Early intervention and Assessment in Community Mental Health – a mental healthcare service set up to work closely with schools, social service agencies and general practitioners (GPs) to help students with emotional, social, and/or behavioural issues within the community.

CHAPTER 6: COMPLEMENTARY AND ALTERNATIVE TREATMENT

6.1 INTRODUCTION

Complementary and Alternative Treatment or Medicine (CAM) therapies refer to healthcare approaches that are not typically part of conventional medical care or that may have origins outside of usual Western practice. 'Complementary medicine' is used *together with* conventional medicine, whilst 'alternative medicine' is used *instead of* conventional medicine. 'Integrative medicine' combines treatments from conventional medicine and CAM for which there is evidence of safety and effectiveness.

Although there is limited evidence of benefit in general, CAM use is common. A systematic review by Hofer (2019) estimates that the prevalence of any CAM use in children and adolescents on the autism spectrum ranged from 28% to 95% (median 54%).[384] Special diets or dietary supplements (including vitamins) were the most frequently used CAM. Locally, CAM use among patients presenting to a paediatric emergency department in Singapore was found to be very common, with 78% reporting having taken a CAM within the previous 12 months, and 18% reporting CAM use on the day of presentation. Vitamin supplements, cod liver oil and probiotics were the most commonly used CAM locally. Of note, CAM use is often not disclosed to the physician.[385]

The number of CAM therapies is growing and research is ongoing and active for many of these therapies. This chapter focuses on the use of CAM to improve core symptoms of autism in children and adolescents on the autism spectrum. CAM interventions which demonstrate no evidence of treatment benefit and/or significant potential for harm "should not be used", while those with insufficient evidence of treatment benefit with no/low potential for harm are "not recommended".

Interventions that children and adolescents undergo should be selected based on evidence from well-designed research, with no potential for harm. Overall, evidence concerning the effectiveness of CAM in autism is insufficient and inconclusive to make strong clinical recommendations with. Studies that report positive findings may have methodological limitations for several reasons: heterogeneous protocols and interventions, small sample size, unclear/absent blinding, variety in placebo conditions, lack of consensus on outcome measures.[386] Moreover, biological plausibility is lacking for many CAM interventions.[387] The theoretical foundations for CAM interventions are often speculative, and may not be supported by reliable observations. Standardised, replicable trials might be especially difficult to conduct in the field of autism, as the population is highly heterogeneous from a clinical, cognitive and social, as well as biological and aetiologic point of view.

When professionals discuss the use of CAM with parents of children and adolescents on the autism spectrum, it is important to explain potential benefits and harms associated with CAM. The decision to use CAM should be guided by evidence of its efficacy and safety in scientific studies employing adequate research design. Therefore, healthcare professionals should keep themselves updated on developments in the field of CAM.[3]

Parents and caregivers should be encouraged not to replace mainstream, evidence-based interventions with CAM.[5] They should be encouraged to discuss their concerns and their child's intervention plans and therapies with their healthcare professional. Decisions to use CAM should take into consideration the following:

1. Whether and in what ways the CAM adds value to an existing mainstream programme;
2. Implications on investing limited resources (i.e., time, money, manpower) on interventions that may not produce desired results and detract caregivers from evidence-based interventions;
3. The potential for harm, especially in the young, growing child with vulnerable neurological and physiological systems.

It may be helpful to distinguish alternative therapies from complementary therapies that build on typical activities of childhood by adding an adapted therapeutic component to make the activity accessible for

children on the autism spectrum. Examples of such complementary therapies may include some forms of physical activity and animal-assisted therapies, music therapy and other therapies that employ creative outlets. It is possible that exposure to these activities will be enjoyable and engaging for the children who likes them. Such activities can allow the child to participate within a community setting and this is consistent with the World Health Organisation (WHO) model of increasing participation and function; regardless of therapeutic value of the activity specific to autism.[388] Table 6.1 summarises the recommendations arising from this chapter for easier reference.

GPP 6.1 ***Professionals should be prepared to discuss the evidence for Complementary and Alternative Medicine (CAM) with caregivers of children and adolescents on the autism spectrum. Shared decision-making on trials of CAM for autism is strongly encouraged between professionals and parents, so that the trials are time-based with clear objectives, outcome measures and endpoints. Parents and caregivers should not replace mainstream interventions with CAM. [EM6-1]***

Table 6.1: Summary of recommendations

Type of recommendation	CAM
CAM that should NOT be used in the treatment of children and adolescents on the autism spectrum	Antimicrobial therapy Aromatherapy Chelation therapy Chiropractic, osteopathy and cranio-sacral therapy Facilitated communication Helminth therapy Hyperbaric oxygen therapy Immunoglobulin therapy Microbial transfer therapy Stem cell therapy Vagal nerve stimulation
CAM that is not recommended as treatment for core symptoms of autism in children and adolescents	Acupuncture Amino acid supplementation Animal-assisted interventions Art therapy Auditory integration therapy Camel milk Coenzyme Q10 Dance movement therapy Digestive enzymes Folinic acid Gluten-free casein-free (GFCF) diet Ketogenic diet Mesalazine Mindfulness intervention Minerals including Zinc, Magnesium and Iron Neurofeedback Omega-3 fatty acids Probiotics Qigong massage or other types of massage Secretin Sulforaphane Transcranial direct current stimulation Vitamins including B12 and B6

CAM that may be considered in children and adolescents on the autism spectrum	Music therapy Visual motor exercises

6.2 NUTRITIONAL APPROACHES

Nutritional supplementation and dietary therapies are the most frequently reported CAM therapies for children and adolescents on the autism spectrum.

6.2.1 Dietary Interventions

Dietary interventions are generally not easy to implement. There is concern about the diversion of resources – for example the time and effort required to prepare the food, ensure compliance to the diet, as well as the costs of special foods and ingredients. Dietary restriction in children on the autism spectrum who may already have rigidity and sensory limitations in feeding, may cause further food refusal. This may lead to nutritional deficiencies.

6.2.1.1 Gluten-Free Casein-Free (GFCF) Diet

Caregivers and families have reported using the GFCF diet. However, the extent of its use is unknown. Apart from rice which is a staple in our Asian diet, it is possible that commercially available gluten-free baked products and the ingredients needed to prepare them are not readily available or are very costly.

The Opioid Excess Theory[389,390] suggests that children on the autism spectrum have a "leaky gut" with insufficient intestinal enzyme activity and hence, gluten and casein are partially digested, leaving big peptides absorbed via the "leaky gut", which was previously believed to be caused by inflammation brought on by Measles, Mumps, Rubella (MMR) immunisation, excessive use of antibiotics and candida overgrowth. These big peptide fragments allegedly travel across the blood-brain barrier and bind to opioid receptors in the brain. It is postulated that the physiology and psychology of autism might be explained by excessive opioid activity linked to these peptides. Another theory was that gluten and casein may provoke adverse autoimmune responses in the gastrointestinal (GI) system. Evidence to support these theories is lacking.

More evidence on the GFCF diet for children on the autism spectrum has become available over the past 10+ years, including meta-analyses and randomised controlled trials (RCTs).[391–401] However, improvements in core symptoms are limited and certainty of the effects is very low. Of note, many of the limitations contributing to study weaknesses are inherent to the intervention delivered and population studied – hence, it should not be expected that more studies would improve the interpretability or generalisability of findings. Reassuringly, no major safety concerns are gleaned from the evidence although this is limited to up to 12 months of data. While the evidence does not support a recommendation for GFCF diet in all children on the autism spectrum, if parents wish to do so, a GFCF diet should only be adopted with professional guidance.[402] Family education, discussion on reasons that parents may wish to adopt a GFCF diet, monitoring, and overall informed consent on expected benefits should be discussed.

R 6.2 ***A GFCF diet is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-2]***

GPP 6.3 ***In children and adolescents on the autism spectrum, a healthy diet of a variety of fresh foods is recommended. Healthcare professionals should be equipped with information on recommended daily allowances of vitamins, minerals and other supplements for children and adolescents (appropriate to their age) and be able to discuss with parents possible benefits and harms of the various supplements and dosages. Intake of vitamins, minerals and probiotics in the form of natural fresh food should be encouraged. [EM6-2]***

6.2.1.2 *Ketogenic Diet*

The ketogenic diet (KD) is a high-fat, appropriate-protein, and low-carbohydrate diet that mimics the fasting state of the body and forces the body to use fat as a fuel source. It is proven beneficial in drug-resistant epilepsy. Some studies have demonstrated that KD improves features of autism, but the underlying mechanisms are not known.[403]

A systematic review (2021)[403] as well as an older systematic review in 2015[404] both suggest a possible beneficial effect of KD in improving behavioural symptoms in autism. Adverse effects of KD are reported to include GI effects (constipation, diarrhoea, vomiting), electrolyte imbalance and metabolic dysfunction. Prolonged adherence to KD may cause vitamin deficiency, osteopenia, neurological dysfunction, atherosclerosis, hepatotoxicity, nephrolithiasis and anemia.[405] KD should only be implemented following discussion with a specialist physician, and with dietician involvement.

R 6.4 ***A ketogenic diet is not recommended as treatment for core symptoms of autism in children and adolescents. However, in children on the autism spectrum who have drug-resistant epilepsy, adoption of a ketogenic diet may be considered. A dietician should be involved in the management and monitoring of a child on a ketogenic diet. [EM6-3]***

6.2.1.3 *Camel Milk*

Camel milk is a traditional food used by the Bedouin and other communities in the Middle East. Camel milk is believed to be better tolerated than milk of other ruminants, with its composition closer in composition to human breast milk. Supporters of camel milk as a therapy for autism claim that the anti-oxidants in camel milk can reduce the levels of reactive oxygen species (ROS) in children on the autism spectrum. However, the causal link between high levels of ROS and autism is not established.[406]

A systematic review (2022)[407] which included four studies concluded that treatment of autism with raw and boiled camel milk resulted in significantly lower Childhood Autism Rating Scale (CARS) scores than the placebo. However, they concluded that more research with larger numbers of children were needed.[407]

R 6.5 ***Camel milk is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-4]***

6.2.2 Nutraceuticals

Nutraceuticals are products derived from food sources or dietary supplements that may claim to provide medical or health benefits, including the prevention or treatment of disease. Proponents of nutraceuticals may see this as a more natural way to accomplish therapeutic results with minimal side effects.

Autism has been reported to be associated with many variations in metabolism, but how these metabolic disturbances correlate with behaviour and development, and their links to other core metabolic disruptions are still not fully understood. As autism is behaviourally and biologically heterogeneous, it is likely that autism may represent a series of conditions arising from different underlying genetic, metabolic and environmental factors.[408]

6.2.2.1 *Vitamin, Mineral & Other Supplements*

Several researchers have noted that patients on the autism spectrum have various metabolic and nutritional abnormalities including issues with sulfation, methylation, glutathione redox imbalances, oxidative stress, and mitochondrial dysfunction. There is some evidence that vitamin and mineral supplementation may support these basic physiologic processes.[409] Levels of vitamins B1, B6, B12, A and D have been reported to be low in children on the autism spectrum.[410]

Atypical eating behaviours and feeding problems, such as food refusal, preferences for a certain product or food, an obsessive routine for taking meals, and preference for the colour and texture of a specific kind of food, are commonly reported by parents of children and adolescents on the autism spectrum.[411] Children and adolescents on the autism spectrum may therefore have micronutrient deficiencies due to poor nutrient intake. This may lead to perturbations in the production of enzymes, hormones or other substances, which are essential for development and maintenance of normal body functioning.

The literature was reviewed for the vitamins, minerals and amino acids that are anecdotally used in Singapore to treat autism and have had more research conducted.

Looking at general vitamin supplementation, an RCT examined the effects of a once-daily multivitamin and mineral supplement.[412] The mean age of the 141 children was 10.8 years and 11% were female. After 13 weeks, there was significant improvement in the Parental Global Impressions scale (Overall/ Hyperactivity/Tantrums/Receptive Language), but not in other measures of features of autism. No significant side effects were reported and the study was of moderate quality evidence.

Wang et al. (2022) reported on Research Progress on the Role of Vitamin D in autism.[413] They found that children and adolescents on the autism spectrum have significantly lower vitamin D concentrations than control group participants and that a few studies have demonstrated that vitamin D appears to help to improve features of autism, but overall, due to different methods, few interventional experiments, and inconsistent results, there is no consensus on the therapeutic effect of vitamin D in autism. Further large sample, randomised double blind trials are needed. Li et al. (2022) conducted a systematic review and meta-analysis which included three RCTs and concluded that vitamin D supplementation appears to be beneficial for hyperactivity but not for core symptoms or other co-existing behaviours and conditions associated with autism.[414]

R 6.6 ***Vitamin supplementation (of any type) is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-5]***

GPP 6.7 ***Children and adolescents on the autism spectrum who exhibit symptoms suggestive of a vitamin, mineral, amino acid or other nutritional deficiency, should be evaluated, treated and monitored following appropriate clinical guidelines. [EM6-5]***

See earlier GPP 6.3.

6.2.2.2 Vitamin B6 and Magnesium

Magnesium is given with vitamin B6, as it is supposed to help the body absorb vitamin B6 and reduce any side effects. Vitamin B6 is important for the synthesis of many neurotransmitters , including GABA, serotonin, dopamine, noradrenalin, histamine, glycine, and D-serine, indicating that vitamin B6 supplementation may enhance many neurotransmitter systems.[415] Nye and Brice's Cochrane Review in 2005 included three studies. Due to the small number of studies, their methodological quality and small sample sizes, no recommendation could made regarding use of B6-Mg as a treatment for autism.[416]

Sato et al. (2018) cites a 2006 report that Vitamin B6 has been documented to be helpful in decreasing behavioural problems in some children on the autism spectrum.[415] Rahman et al. (2021) reports on a randomised double blind placebo-controlled trial with 70 participants.[417] This study revealed an overall improvement in the features of autism along with improvements in the specific domains of Emotion and Cognition.

R 6.8 ***Vitamin B6 is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-6]***

6.2.2.3 Folinic Acid

Folinic acid is a naturally occurring, reduced form of folic acid; it is currently used regularly as an adjuvant medication to many chemotherapy agents and also in the treatment of methotrexate toxicity.

There is a small body of evidence, at present, regarding the use of folinic acid for the treatment of autism. This encompasses a small number of randomised studies (two double blind RCT and one single blind RCT)[418–420] as well as several open-label trials, each with notably small sample sizes.[421,422] Overall, while the results of these studies suggest beneficial effects on symptoms of autism and communication, the quality of evidence is low to moderate in nature. However, the side effect profile of folinic acid is good with minimal adverse effects and it has been used within the medical field for other conditions for many decades now. As such, larger trials on the subject may lead to more conclusive evidence illustrating the beneficial effects of folinic acid in future. At present, there is insufficient evidence to support routine use of folinic acid as a treatment modality for the core symptoms of autism.

R 6.9 ***Folinic acid is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-7]***

6.2.2.4 Vitamin B12

Vitamin B12 is an essential cofactor in methionine transmethylation/transsulfuration metabolism. Rossignol et al. 2021 reported a systematic review and meta-analysis on the effectiveness of cobalamin (B12) treatment for autism.[423] Seventeen studies with a total participant number of 565 were identified. Of these, only four studies were double-blind placebo-controlled studies, with 248 participants. However, only a few studies used standardised outcomes. This made it impossible to perform a meta-analysis across clinical outcomes. Overall, their conclusion was that B12 appears to have evidence for effectiveness in individuals on the autism spectrum, particularly in those who have been identified with unfavourable biochemical profiles. Adverse effects identified by the meta-analysis included hyperactivity (11.9%), irritability (3.4%), trouble sleeping (7.6%), aggression (1.8%), and worsening behaviors (7.7%), but these were generally few, mild, not serious and not significantly different compared to placebo.[423]

R 6.10 ***Vitamin B12 is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-8]***

6.2.2.5 Mineral Supplementation

Cross-sectional, case-control studies have suggested differences in the levels of minerals like magnesium in individuals on the autism spectrum as compared to typically developing individuals; these are of low-quality evidence.[416,424] There is a lack of high-quality evidence supporting the routine use of mineral supplements in children and adolescents on the autism spectrum. A single RCT from 2011 showed beneficial effects of a supplement that contained more than 10 different vitamins and minerals including magnesium and this was of moderate-quality evidence.[425] There have been no other recent trials examining this clinical question specifically. While the safety profile of supplements in research studies is good with no major adverse effects, there is potential for harm by using mineral supplementation at high doses without appropriate monitoring in real-world settings and this can lead to toxicity for example of iron or magnesium. Hence, mineral supplementation is not recommended to address core symptoms of autism. Specific individuals with documented iron deficiency (which is a common medical condition in the general paediatric population) should be treated with iron therapy as per standard dosing guidelines and with appropriate regular blood monitoring.

R 6.11 ***Supplementation with zinc, magnesium, iron or any other minerals is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-9]***

See earlier GPP 6.3 and R 6.7.

6.2.2.6 Amino Acid Supplements

It has been hypothesised that children on the autism spectrum may have deficiencies of amino acids, or have different metabolic processes. The Children's Autism Metabolome Project (CAMP) is an

ongoing, large-scale effort to define autism biomarkers based on metabolomic analyses of blood samples from young children; this is based on evidence that dysregulation of branched-chain amino acids (BCAAs) may contribute to the behavioural characteristics of autism.[426]

Chen et al. (2022) recently reported on the plasma amino acid profiles of 110 children diagnosed with autism in Southern China (versus 55 controls).[427] Elevated neuroactive amino acids (glutamate) and decreased essential amino acids were mostly distinct characteristics of plasma amino acids of children on the autism spectrum. Increased level of tryptophan might be associated with severity of autism. Dimethylglycine (DMG) supplementation was shown to have a positive treatment response in a single study reported in 2001, but the quality of evidence was regarded as very low.[428] A recent paper by Dhanjal et al. (2021) adds no evidence apart from a single case description in 2011.[429]

L-carnitine plays an important role in the functioning of the central nervous system, and especially in the mitochondrial metabolism of fatty acids. Altered carnitine metabolism, abnormal fatty acid metabolism has been documented in some patients on the autism spectrum. L-carnitine supplementation may be beneficial in alleviating behavioural and cognitive symptoms in this subgroup of patients with changes in their acylcarnitine profiles.[429] In the review by Malaguarnera et al. (2019), findings from two RCTs and one open-label prospective trial suggest that carnitine administration could be useful for treating symptoms in non-syndromic autism.[430]

L-glutamine is traditionally considered a non-essential amino acid that is thought to be an antioxidant, with important physiological functions. Shimmura et al. (2011) studied the plasma levels of 25 amino acids in 23 male children on the autism spectrum and 22 male controls. They found that the autism group had higher levels of plasma glutamate and lower levels of plasma glutamine. No significant group difference was found with the remaining 23 amino acids.[431] A more recent paper from Cochran et al. (2015) suggests an imbalance between glutamatergic neurotransmission and GABA-ergic neurotransmission in autism. Higher glutamine levels and lower GABA/Cre levels were associated with lower IQ and greater difficulties in social cognition across groups.[432] Overall, there is insufficient information to recommend use of L-glutamine to improve core symptoms of autism.

L-carnosine is an amino acid which has been proposed to have neuroprotective, antioxidant and anti-convulsive properties that may benefit children on the autism spectrum. The meta-analysis by Abraham et al. (2021) showed no significant difference between the L-carnosine and placebo groups in the Gillian Autism Rating Scale and the CARS. They concluded that current data does not support the use of L-carnosine in the management of children on the autism spectrum due to a low number of studies and sample size available. Further studies are warranted to know the effect of L-carnosine for autism management.[433]

R 6.12 ***Amino acid supplementation is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-10]***

See earlier GPP 6.3 and R 6.7.

6.2.2.7 Omega-3 Fatty Acids

Omega-3 fatty acid supplementation for children on the autism spectrum has been increasingly studied in RCTs over the past 10 years.[434–446] A pooled meta-analysis of these studies showed that overall, children who had Omega-3 supplementation showed some reduction in irritability. There were non-statistically significant improvements in other autism-related symptoms, such as lethargy, inappropriate speech, hyperactivity, social motivation, social cognition, social, and functional communications. However, these findings were limited by small sample sizes, generalisability issues, confidence in effect estimates, and lack of long-term data, thereby limiting the confidence in the reported effects. Differences in outcome scales used and use of self-reported endpoints also affected evidence quality. Nevertheless, no major safety concerns were found with the use of Omega-3. While the evidence may not be able to support a recommendation for Omega-3 supplementation in all children on the autism spectrum, positive (albeit non-statistically significant) trends across some of the outcomes and lack of major safety

concerns could position Omega-3 supplementation as part of shared decision-making with parents or caregivers. Family education, discussion on reasons that parents may wish to adopt Omega-3 supplementation, monitoring, and overall informed consent on expected benefits should be discussed.

R 6.13 ***Omega-3 fatty acid in any form or combination (including with phosphatidylserine) are not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-11]***

6.2.2.8 Probiotics

There is a rapidly growing body of research looking at the role of the gut-brain axis in autism, and the role of various therapies aimed at modifying the gut microbiota. These therapies include probiotics, dietary alterations, antibiotics and microbial transfer therapy (MTT).

The gut-brain axis refers to the bidirectional communication between gut microbes and the brain. In addition to aiding digestion, it has been found that gut microbes also manufacture bioactive compounds that help to orchestrate brain function and social development. In autism, it is hypothesised that probiotics alter brain function by its activity in restoring the healthy balance of the intestinal microbiota and modulating the levels of neurotransmitters.[447]

Studies have shown that children on the autism spectrum often have a mix of gut microbes that is distinct from that in children without autism. However, there is a lack of consistency in the reported gut microbiome changes in these studies. Of note, the gut biome is also known to vary based on geographical location, possibly impacted by foods eaten, soil and water of the locality.[448]

Overall, findings from several systematic reviews appear to suggest limited, but preliminary evidence of efficacy in relieving GI distress, improving autism-associated behaviours, altering microbiota composition, and reducing inflammatory potential.[449] The efficacy of probiotics is known to be strain- and condition-specific. Large scale, well-designed studies are needed to confirm this. However, if parents wish to use probiotics, family education, discussion on reasons for use, monitoring, and overall informed consent on expected benefits should be discussed.

R 6.14 ***Probiotics are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-12]***

6.2.2.9 Digestive Enzymes

Use of digestive enzymes to treat autism is based on the opioid excess theory, which suggests that there is insufficient intestinal enzyme activity and hence, gluten and casein are partially digested, leaving its big peptides absorbed via a leaky gut, which may be caused by GI inflammation brought on by excessive use of antibiotics and candida overgrowth.[450] These peptide fragments travel across the blood-brain barrier and bind to neurotransmitter sites in the central nervous system as endogenous opioids. It is postulated that the physiology and psychology of autism might be explained by excessive opioid activity linked to these peptides. However, this theory has been debunked. If children on the autism spectrum are not turning peptides into amino acids, then more peptides should be present in their urine. No significant differences were found between the urinary peptide profiles of children on the autism spectrum and their typically developing peers.[451]

Saad et al. (2015) conducted a double-blind RCT on 101 children on the autism spectrum – the group receiving digestive enzyme therapy for 3 months showing significant improvements in emotional response, general impression autistic score, general behaviour and GI symptoms, with the CARS applied to both groups.[452] They concluded that digestive enzymes were inexpensive, readily available, had an excellent safety profile and showed at least mildly beneficial effects in children on the autism spectrum. An earlier double-blind RCT by Munasinghe et al. (2010) to examine the effects of digestive enzyme supplementation for autism did not show clinically significant effects on improvement of autism symptoms with enzyme use. However, a small, statistically significant improvement with enzyme

therapy was seen for the food variety scores. They concluded that this warranted further detailed investigation.[453]

6.2.2.10 Secretin

Secretin is a GI hormone that helps to promote digestion of food. It was first presented as an effective treatment for autism in 1998 based on anecdotal evidence, in which a child with autism undergoing endoscopy to investigate his severe diarrhoea was given secretin. After the endoscopy, he appeared to make remarkable improvements, smiling and talking for the first time. His parents believed that the secretin was the cause of those improvements.[454] Secretin is believed to have a role in decreasing immune responses in the gut lumen. Secretin receptors have also been demonstrated in the brains of rats and pigs, but the exact role of secretin and its mechanism of action in the central nervous system have not been determined. There is uncertainty about the role of secretin in the human brain.[455]

A systematic review (2011)[456] and a Cochrane review (2012)[455] both concluded that there was no evidence that secretin was effective in improving the core symptoms of autism.

R 6.15 ***Secretin and digestive enzymes are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-13]***

6.2.2.11 Sulforaphane

Sulforaphane is found in broccoli, mostly in the sprouts, and partially inactivated by cooking; some studies suggest it may improve symptoms of autism. Though the exact mechanisms of action are not fully understood, sulforaphane may target several physiological mechanisms implicated in autism, such as redox metabolism/oxidative stress.

There is ongoing research in the use of sulforaphane in the treatment of children on the autism spectrum. A systematic review (2020) included five studies of sulforaphane and concluded that sulforaphane was a safe and effective supplement in treating autism; however, all the studies were small.[457] A recent study by Ou et al. (2022) on a cohort of 108 children in China showed no significant changes in caregiver rated global impression scales between sulforaphane and placebo groups.[458] However, clinician rated scales showed a significant improvement in the sulforaphane group, and one third of participants showed at least a 30% decrease in autism severity score after 12 weeks of treatment. The effects of sulforaphane were seen across the full range of intelligence and greater in participants over 10 years. Sulforaphane was safe and well-tolerated even for young children. However, the inconsistent results between caregiver and clinician rated scales suggest that more clinical trials are needed to confirm the findings.

R 6.16 ***Sulforaphane is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-14]***

6.2.2.12 Coenzyme Q10

Coenzyme Q10 (CoQ10; ubiquinol) is marketed extensively as “a naturally occurring chemical that exists in almost every cell of the human body, carrying out several vital roles, including promoting energy production and neutralising harmful particles called free radicals.”

Emerging research has suggested that mitochondrial dysfunction may play a role in the pathogenesis of some patients on the autism spectrum, with evidence for increased levels of oxidative stress and reduced antioxidant capacity. Some children on the autism spectrum have been shown to have depressed ubiquinone, suggesting that supplementation with ubiquinol may be therapeutic for at least a subgroup of these children.[459]

Only two studies have been carried out using CoQ10 alone. In a small double-blind placebo-controlled study, a low dose of ubiquinol (30–60 mg) improved GI problems and sleep disorders as well as markers of oxidative stress in children on the autism spectrum.[460] In another small open-label study, ubiquinol

(100 mg) improved communication, playing, sleeping, and food rejection in a minority of study participants if the CoQ10 plasma level was above 2.5 µmol/L.[461]

There appears to be little evidence that CoQ10 is effective in improving core symptoms of autism, although there is some evidence it may help with sleep.[462]

R 6.17 ***Coenzyme Q10 is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-15]***

6.2.3 Other Biologically-based Therapies

6.2.3.1 Antimicrobial Therapy

Intestinal dysbiosis and immune dysregulation in children on the autism spectrum were thought to contribute to autism symptoms. Antibiotics such as vancomycin and antifungals such as fluconazole and nystatin have been used to treat autism. The rationale for the use of antibiotics is to rid the gut microbiome of bacteria that may produce neuroactive substances which cause negative behaviours via the gut-brain axis. Currently, there is a plethora of research characterising gut microbiota in children on the autism spectrum, but the results cannot confirm a global or consistent microbiome change in these children. Children on the autism spectrum have been shown to have an overall less diverse microbiota. However, the use of empiric antibiotic therapies is, at this point, still unproven. Oral vancomycin has been used in the treatment of autism[463–465] but there are no reports of controlled trials. Vancomycin is also known to be associated with nephrotoxicity and ototoxicity, and the risk of antibiotic resistance and allergic reactions and anaphylaxis.

Use of antifungal therapy is based on a theory that some children on the autism spectrum may have yeast overgrowth, which releases neuroactive substances and contributes to their behavioural differences.[466,467] The yeast overgrowth is said to stem from multiple episodes of antibiotic use in infancy and early childhood, but this theory has not been proven. There have been no controlled trials of antifungal or anti-yeast therapies for children or adolescents on the autism spectrum. There is a risk of hepatotoxity with fluconazole use and diarrhoea with nystatin use.

R 6.18 ***Antimicrobial therapy should not be used in the treatment of core symptoms of autism in children and adolescents, as there is potential for harm, and no evidence of benefit. [EM6-16]***

6.2.3.2 Microbial Transfer Therapy (MTT)

There is growing evidence to support the possibility of an altered gut microbiome profile among individuals on the autism spectrum (compared to healthy controls) and how this may contribute to symptoms of autism, especially relating to behavioural difficulties. Hence, there has been exploratory research done in animal studies and a handful of human trials looking at a treatment role of MTT for individuals on the autism spectrum.[468–470] The human studies used faecal microbial transplantation, i.e., use of faecal microbiota from a healthy donor for treatment. However, both studies are of low-quality evidence with high risk of bias, as they are open-label in nature without placebo control. There is thus insufficient evidence currently to draw meaningful conclusions and warrant MTT as a treatment modality. Further large-scale RCTs are required on this topic.

R 6.19 ***Microbial transfer therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-17]***

6.2.3.3 Helminth Therapy

Helminth therapy refers to the intentional ingestion of helminth (worm-like) parasites of various types such as roundworm, tapeworm and hookworm. This is not an established treatment for any medical condition currently with no high-quality evidence to support its use. It has been proposed as a potential treatment for autoimmune disorders such as inflammatory bowel disease (specifically Chron's disease

and ulcerative colitis), eczema and asthma due to the potential for helminths to reduce/alter the immune response and hence have beneficial effects in these conditions. By the same accord, there have been propositions that such therapy might be useful in autism, given emerging research in the role of the immune system in autism.

However, helminth therapy has not been scientifically studied in autism, apart from one RCT in adults on the autism spectrum, with no evidence base to support its use.[471] Parasite infections are also known medical conditions with numerous ill-effects including anaemia, systemic infection and weight loss. Hence such a therapy carries potential for significant adverse effects.

R 6.20 ***Helminth therapy (in any type or form) should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-18]***

6.2.3.4 Mesalazine

Inflammatory bowel disease (IBD) has been found to be more prevalent in children on the autism spectrum compared to controls, and there is an association between autism and IBD. They are 47% more likely to have Crohn's disease and 94% more likely to have ulcerative colitis.[472] A recent systematic review and meta-analysis confirms this association.[473] A 2022 paper has found evidence of a potential causal link between parental, particularly maternal IBD and autism in children.[474]

Mesalazine is a drug used to treat IBD. No research on the use of mesalazine in treating autism has been published.

R 6.21 ***Mesalazine is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-19]***

(See also Chapter 7, R 7.13)

R 7.13 ***Healthcare professionals should be aware that children and adolescents on the autism spectrum have a higher occurrence of gastrointestinal conditions. Referrals for thorough evaluation should be made for those who present with persistent or recurrent gastrointestinal symptoms, such as colic or recurrent abdominal pain, vomiting, nonspecific diarrhoea, or constipation. [EM7-11]***

6.2.3.5 Immunoglobulin Therapy

There has been some evidence suggesting an association between autism and immune disorders including maternal auto-immune conditions. Individuals on the autism spectrum have been noted to have abnormal levels of immunoglobulin in their blood as well as inflammatory cytokines in a few low-quality studies. Hence, the role of immunoglobulins as treatment for autism has been studied. However, there has only been one placebo-controlled study looking at the use of immunoglobulins and this did not demonstrate any clear beneficial effects on the symptoms of autism.[475] Another systematic review which included children with immune conditions and autism did not find conclusive results as well.[476] Immunoglobulin is no longer studied as a potential treatment in children on the autism spectrum and in other immune disorders in the recent literature from 2010 onwards. Therefore, there is no evidence base for recommending the use of immunoglobulins for children and adolescents on the autism spectrum.

R 6.22 ***Immunoglobulin therapy (in any form of administration) should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-20]***

6.2.3.6 Stem Cell Therapy

There have been several studies, primarily in the last 5 years that have investigated the effect of stem cell administration in children on the autism spectrum. Studies have varied significantly in terms of type

of cells administered (umbilical cord blood cells, mononuclear cells or mesenchymal stem cells from bone marrow), infusion modality (intravenous or intrathecal) and treatment protocols (frequency of administration and follow-up period). Overall, the findings from these studies are not consistent with regard to the beneficial effects of stem cell administration on the core symptoms of autism.[477–479] Importantly, studies of high quality with low risk of bias failed to show any beneficial effects across a variety of outcome measures.[480–483] The few studies which have reported beneficial effects have small sample sizes, have a high risk of bias and/or are open-label, non-blinded studies.[484–486] Also notably, intrathecal administration of stem cells has been associated with significant adverse events related to the procedure including backache, headache and vomiting. Intravenous infusions have a better side effect profile with no major adverse events reported.[487] Further, there are significant costs and procedure-related resources involved in stem cell therapy. Hence, at present, there is insufficient evidence to suggest any beneficial effects of stem cell therapy for children and adolescents on the autism spectrum.

R 6.23 ***Stem cell therapy (in both intravenous and intrathecal forms) should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm. [EM6-21]***

6.2.3.7 Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) involves placement of an individual in a high-pressurised chamber of air, where the air pressure is 2 to 3 times that of normal. This is meant to increase the amount of oxygen inhaled into the body and this has been purported to have beneficial effects. HBOT is a known treatment for decompression sickness following diving and also for treatment of specific infections and wounds.

Multiple studies including RCTs over the last decade have not shown consistent benefits in the use of HBOT in managing symptoms of autism; moreover, significant adverse effects of potential ear barotrauma have occurred at a significantly higher rate in patients who received HBOT compared to controls.[488–493] Typically, HBOT was administered over 1-hour sessions in a high-pressurised chamber for a pre-defined period of time on a weekly basis. The quality of evidence showing lack of beneficial effects is low while one study which was of moderate quality showed a potential beneficial effect.[494–496] However, there is a clear potential for harm given the single moderate-quality study that showed greater risk of adverse effects in the HBOT group. Hence, there is no clear benefit for recommending the use of HBOT for children and adolescents on the autism spectrum.

R 6.24 ***Hyperbaric oxygen therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-22]***

6.2.3.8 Chelation Therapy

It has been hypothesised that children and adolescents on the autism spectrum have a higher proportion of systemic heavy metals compared with peers. These higher levels of mercury and other heavy metals are believed to interfere with the developmental process and therefore lead to autism. Chelation therapy involves the use of a pharmacological agent (e.g., DMSA) that binds to the excess heavy metal, leading to its excretion.[497] This causal link between heavy metals and autism has not been established (See Chapter 2, Section 2.3).[157]

A systematic review and a Cochrane systematic review both conclude that there is no evidence to suggest that chelation therapy is an effective intervention for autism.[157,498] Prior reports of serious adverse events including reported death also led to the US Federal government suspending enrolment for clinical trials testing chelation therapy.[499]

R 6.25 ***Chelation therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-23]***

6.2.3.9 *Neurofeedback*

Neurofeedback is a neurological-based therapy which seeks to enhance brainwave patterns by providing the patient with auditory or visual feedback when performing a task. The patient is provided with positive reinforcement when the brain wave frequency changes to a desired level. Real-time functional magnetic resonance imaging (rtfMRI) or electroencephalography (EEG) technology is utilised in neurofeedback techniques, however, only EEG has been used with autism. This technique involves electrode sensors that are placed on the scalp or ear lobes and information on the electrical activity of the brain cortex is recorded.

Existing guidelines and literature on the effect of neurofeedback in the treatment for autism have shown a low magnitude and certainty of effects due to small sample sizes, lack of standardised outcome measurements and a lack of studies with RCTs.[500,501] Currently, there is also no optimised treatment protocol developed to provide guidelines for professionals on the use of neurofeedback as a treatment for autism.[502]

In a systematic review conducted by Van Hoogdalem et al. (2021), 19 out of 20 studies reviewed showed positive outcomes.[502] Of which, only three of these studies were RCTs. These studies showed positive effects of neurofeedback on the treatment of autism in the areas of social awareness, social communication, attention and sensory motor skills. Two of the RCTs also showed longitudinal effects up to 1 year of follow-up in the areas of social behaviour and executive function.

While the current literature shows promising results, the following areas need to be examined in greater depth: a possible difference in effect of neurofeedback on gender in relation to autism, the optimal number of sessions for effects of neurofeedback to be observed, a common optimal protocol of the use of neurofeedback in autism, and the possibility of a patient-directed model in neurofeedback.

R 6.26 ***Neurofeedback is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-24]***

6.2.3.10 *Vagal Nerve Stimulation*

Vagal nerve stimulation (VNS) refers to the intentional stimulation of the vagus nerve and is delivered by a pulse generator that is implanted in the neck; this is connected to an electrode that can release electrical impulses at pre-set intervals and thus stimulate the vagus nerve. VNS has been shown to increase firing of serotonergic and adrenergic neurons and result in beneficial effects in treatment of severe depression and refractor epilepsy. As such, VNS is currently approved by the US Food and Drug Administration for the treatment of medication-resistant depression and epilepsy disorders. However, there are several side effects associated with VNS, including the surgical risk of the implantation procedure (excessive bleeding, accidental injury to surrounding structures, device migration), as well as results of chronic overstimulation of the vagus nerve including cough, voice alteration, dyspnoea, upper airway narrowing, worsening of obstructive sleep apnoea and bradycardia. As an invasive procedure, VNS is thus seldom used even for epilepsy and depression and is often a last-resort treatment.

VNS has been proposed to have potential beneficial effects in autism, as some observational studies have suggested that the atypical facial reactivity and speech difficulties seen in autism may be associated with reduced vagal tone and dysregulation of the parasympathetic response. Data suggesting that VNS improved mood and quality of life in patients with refractory epilepsy and autism was also used to hypothesise a role for VNS in the treatment of autism. However, there has been no RCTs or even cross-sectional studies examining the use of VNS in individuals on the autism spectrum alone. The current evidence is of very low quality and is limited to small case series and case reports of individuals on the autism spectrum and epilepsy or other syndromes, with some beneficial effects of VNS on mood and quality of life.[503] Hence, there is insufficient evidence to support the use of VNS in autism. Since VNS is an invasive and long-term procedure, there are significant adverse effects associated with it and thus should not be recommended or performed for autism.

R 6.27 ***Vagal nerve stimulation should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm, and no evidence of benefit. [EM6-25]***

6.2.3.11 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which claims to modulate excitability in different regions of the cerebral cortex and produce after-effects on neuron excitability that can last from minutes to hours when the stimulation is applied over a prolonged period. There is growing evidence suggesting that socio-communicative, cognitive and sensori-motor differences are related to abnormalities of distributed networks.[504] tDCS seems to be able to modulate the brain's functional connectivity.

A systematic review of the use of tDCS in autism appeared to show improvement in socialisation, repetitive behaviours, sensory difficulties and cognitive awareness and health problems.[505] There were also some benefits in cognitive and language. However, the included studies were of low quality, with methodological issues. Randomised, double-blind trials as well as standard evaluation protocols are needed.

R 6.28 ***Transcranial direct current stimulation is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-26]***

6.2.4 Mind and Body Practices

The therapies in this section are non-ingestible and to some, considered non-biological. They comprise physical therapies; acupuncture; sensory therapies like vision and auditory therapies; therapies with mind-body components like yoga, qigong, art; creative therapies (art, music, dance); and psychological therapies like mindfulness interventions.

6.2.4.1 Auditory Integration Training/Sound Therapies

Auditory integration therapy (AIT) was developed as a technique for improving abnormal sound sensitivity in individuals with behavioural disorders including autism. AIT is offered to children on the autism spectrum on the premise that they experience discomfort when listening to certain sound frequencies. In AIT, the participant listens to modulated music tapes through headphones for a specified time period.

Other sound therapies bearing similarities to AIT include the Tomatis Method and Samonas Sound Therapy. A review of literature revealed risk of bias present in most of the studies – a high level of heterogeneity and disparate outcome measures used. Authors of the Cochrane Systematic Review note the implications for practice, which include consideration of hearing loss and that parents need to also be aware of cost.[506]

There is insufficient evidence to support the use of AIT at this time.

R 6.29 ***Auditory integration therapy and other sound therapies are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-27]***

6.2.4.2 Music Therapy

Music therapy uses musical experiences and relationships that develop through these experiences, which allow people to relate to others and communicate, thus engaging on a more emotional, relationship-based level than what is accessible through verbal language. Music therapy thus attempts to address the core symptoms of autism.

Existing guidelines and previous studies were inconclusive and called for larger sample sizes and standardised outcome measurements so that long-term effects can be examined.[507–512] However, in the most recent systematic review by Geretsegger et al. (2022), there is moderate certainty of evidence

that music therapy was specifically associated with an increased chance of global improvement for autistic people, likely helps them to improve total autism severity and quality of life, and probably does not increase adverse events immediately post-intervention.[513] There is no clear evidence for the outcome areas of social interactions, non-verbal communication, and verbal communication. There is scope to explore the effects of music therapy beyond the young adult age, as well as to investigate the longitudinal effects of music therapy as a treatment approach in autism.

R 6.30 ***Music therapy may be recommended as a complementary intervention approach for children and adolescents on the autism spectrum. Specifically, there is moderate level of evidence for an increased chance of global improvement, improved quality of life and reduced total autism severity. [EM6-28]***

6.2.4.3 Dance Movement Therapy

Dance/movement therapy (DMT) refers to the psychotherapeutic use of movement to promote emotional, social, cognitive and physical integration of the individual, for the purpose of improving health and well-being.[514] There is currently insufficient evidence to support the use of DMT for children on the autism spectrum.[515–517] Studies are limited and often of small sample sizes and low quality.[515–517] Emerging literature is demonstrating the potential of DMT in promoting well-being and improving social communication skills in these children.[516,517] However, more research is warranted to establish the effectiveness of DMT.

R 6.31 ***Dance movement therapy (DMT) is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-29]***

6.2.4.4 Art Therapy

Art therapy is defined in this context as a psychological discipline that focuses on using visual art-making to help bring about therapeutic changes in clients.[518] Schweizer et al. (2014) conducted the only systematic review of art therapy in children on the autism spectrum and concluded that studies of art therapy in this population were generally weak in methodological quality and highly biased.[519] However, findings were generally positive with qualitative analyses suggesting that art therapy "may contribute to a more flexible and relaxed attitude, a better self-image, and improved communicative and learning skills in children on the autism spectrum."

Cohen-Yatziv and Regec (2019) conducted a more recent systematic review of the effectiveness of art therapy with children in general.[518] The authors acknowledged that they "only found a small number of quantitative studies that relate to the effectiveness of art therapy with children, despite the growing need for this type of therapy" and concluded that there is "much needed research in the field of art therapy with children". They could only find 13 quantitative studies, of which only one study involved children on the autism spectrum. This dearth of evidence renders it impossible to recommend art therapy as a therapeutic intervention targeting the core symptoms of autism.

Art therapy is an easily available intervention much sought after by caregivers of children on the autism spectrum. Although there is insufficient empirical evidence supporting the effectiveness of art therapy in treating the core symptoms of autism, there is a need to appreciate that for a selected group of children on the autism spectrum, art therapy may enhance their participation in the community and enhance their well-being and quality of life.

R 6.32 ***Art therapy is not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-30]***

6.2.4.5 Vision Therapies

Sensory processing difficulties are often found in children on the autism spectrum and this may result in visual-related difficulties such as photosensitivity, colour perception processing, differences in central

and peripheral stimuli processing, facial processing, gaze shifts, visual integration with other senses, visual closure and other visual-motor processing and visual spatial awareness.[520] (*See Chapter 7, section 7.5.10 on visual challenges in autism)*

In individuals with visual processing difficulties, some treatment options include refractive correction, plus lenses, adds, and yoked prism lenses, as well as coloured overlays / filters, coloured lenses, optometric vision therapy, visual perceptual and visual motor training, and environmental modifications.[521,522] It appears that improved visual processing for some children on the autism spectrum may result in the improvement of core symptoms of autism.

This may have prompted the trial of different types of vision therapy in attempts to improve the core symptoms of autism. However, there are few studies researching the use of vision therapy in children on the autism spectrum. From the few studies conducted so far, there appears to be emerging evidence that vision therapy, especially in the form of visual-motor exercises, may have a positive effect on the visual processing, social communication and reduction of repetitive behaviours of children on the autism spectrum. No adverse effects have been reported on the use of vision therapy in this population so far.

Nevertheless, as the number of studies is small and the level of evidence low, there is currently insufficient evidence to support the benefits that vision therapy may have on core symptoms of autism in children and adolescence on the autism spectrum. For many children on the autism spectrum, having co-occurring visual-related difficulties could further aggravate their issues with social communication and unusual behaviours. In such instances, visual motor exercises may be considered as a treatment for these selected children who present with visual-related difficulties.

R 6.33 ***Vision therapy is not recommended as treatment for core symptoms of autism in children and adolescents. However, visual motor exercises may be considered for selected children on the autism spectrum who have visual difficulties as there is emerging evidence that such exercises have the potential to improve social communication and reduce repetitive behaviours. [EM6-31]***

6.2.4.6 Aromatherapy

Essential oils are plant extracts that retain the properties of the plants from which they are extracted, such as lavender, lemongrass, eucalyptus, geranium, cinnamon, tea trees, and peppermint. Essential oils can be applied using various ways, including vaporisation (aromatherapy), topical application or consumption.[523] In general, publications about the effects of essential oils on children on the autism spectrum suggested that essential oils may be useful in improving quality of life,[524] promoting sleep,[524] calming anxiety and reducing stress[524–526] and facilitating learning, communication and interaction with others.[523]

Dolah et al. (2022) reviewed the literature on essential oils and aromatherapy in an attempt to understand their effect on children on the autism spectrum.[523] Most studies were conducted on healthy individuals, for whom there appears to be a beneficial effect on learning. Most of the evidence is anecdotal or from case series. The authors concluded that there is insufficient evidence to recommend the use of essential oils and aromatherapy to improve the key outcomes of children on the autism spectrum, including quality of life, sleep and anxiety.

There have been reports of adverse effects when essential oils are administered in various forms on children and adolescents. These include skin irritation, photosensitivity, airway irritation, with some reports linking use of essential oils to prepubertal gynecomastia and seizures.[527] Studies indicating that use of essential oils is safe and effective in the paediatric population are currently lacking.

Children on the autism spectrum may have unusual sensory responses, and may perceive odours to be more intense and less pleasant than children who do not have autism. Bergamot aromatherapy oils have been shown to reduce anxiety in healthy individuals and adults. The effects this oil has on medical office-induced anxiety in 6–11 year old children on the autism spectrum were observed in a randomised

blinded clinical trial. The authors of this study cautioned that exposure to bergamot essential oil has the potential to increase, rather than decrease, feelings of anxiety in these children.[528]

R 6.34 ***Aromatherapy should not be used as treatment for core symptoms of autism in children and adolescents, as there is potential for harm. [EM6-32]***

6.2.4.7 Acupuncture

Acupuncture is a traditional Chinese Medicine procedure in which specific body areas (acupoints) are pierced with fine needles for therapeutic purposes. It is believed stimulating the acupoints will correct the disharmony and dysregulation of organ systems, which might manifest as symptoms of autism.[529]

In recent years, a vast body of research (i.e., RCTs[530] and systematic review papers[531–534]) has investigated the effects of acupuncture on mitigating the core symptoms of autism. Positive findings on various outcomes have been reported at the single study level. However, as noted in the review papers, there are considerable inconsistencies across outcomes and studies. Besides inconsistencies, several methodological issues – including small sample sizes, high heterogeneity among participants and treatment protocols, allocation and concealment bias – moderate the certainty about the effects of acupuncture intervention for children and adolescents on the autism spectrum. Given the inconsistency in findings and methodological limitations, the existing literature on acupuncture and autism provides low to very low levels of evidence supporting the effectiveness of acupuncture as the primary intervention strategy or a complementary intervention in treating the core symptoms of autism. There is limited data available on the safety of acupuncture treatment for children on the autism spectrum.

R 6.35 ***Acupuncture is not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-33]***

6.2.4.8 Massage Therapy

Massage therapy is a group of intervention techniques involving another person applying appropriate pressure to various parts of the client's body. Traditional Chinese massage, traditional Thai massage or Indian massage, and Swedish massage are the most common types of massage.[535] Qigong massage is a sensory-based intervention derived from Chinese Medicine that targets normalising the individual's tactile responses.[536]

Reviews of available literature and existing clinical guidelines from other countries indicate insufficient evidence to support the use of massage or Qigong massage intervention in reducing core symptoms of autism or improving motor skills and adaptive functions. A small body of research has evaluated the effects of Qigong massage.[536–539] These studies report positive outcomes, with some employing randomised control study design. Positive effects on reducing overall autism symptomology were reported at the single study level. However, the quality of the evidence is considered low due to high risk of bias, small sample size, and possible publication bias. Similar methodological limitations were identified among studies included in the reviews.[535]

R 6.36 ***Qigong massage or other types of massage are not recommended as treatment for core symptoms of autism in children and adolescents. [EM6-34]***

6.2.4.9 Chiropractic, Osteopathy and Cranio-sacral Therapy

Chiropractic involves spinal adjustment, manual therapy on other joints, soft tissue manipulation and sometimes exercises, massage and lifestyle counselling to restore health. Cranio-sacral therapy is based on the theory that gentle manipulation of the spine, skull and related soft tissues restores dysfunction in the rhythmic fluctuations of the cerebro-spinal fluid, soft tissue and cranium. Osteopathy involves moving a person's muscles and joints using massage and physical manipulation to improve well-being and treat health problems.

There is insufficient evidence to support the effectiveness of chiropractic, osteopathy and cranio-sacral therapy for children and adolescents on the autism spectrum.[540,541] For chiropractic and osteopathy,

most studies are single-case design and even though there are some positive results, the study quality was poor and insufficient to demonstrate effectiveness. As for cranio-sacral therapy, there are no experimental studies found between 2011–2022 that examine the effectiveness in children on the autism spectrum.

In addition, adverse events such as death or serious injury due to chiropractic and other manual therapies have been reported.[542] In view of the lack of benefits and potential for harm, chiropractic, osteopathy and cranio-sacral therapy are not recommended as therapeutic or complimentary intervention for children and adolescents on the autism spectrum.

R 6.37 ***Chiropractic, osteopathy and cranio-sacral therapy should not be used in the treatment of children and adolescents on the autism spectrum, as there is potential for harm. [EM6-35]***

6.2.4.10 Physical Activity

Physical activity involves the use of physical exertion to improve skills, task performance or behaviour. Examples of physical activity includes running, jumping, climbing, aerobic exercises, swimming, obstacle courses, ball games, yoga, martial arts and other sporting/recreational activities.

There is increasing evidence in the effectiveness of physical activity in addressing core features of autism and improving sensory-motor and social participation outcome in the past 10 years, including a recent meta-analysis that reported a large treatment effect of physical exercise intervention on reducing stereotyped motor behaviours in children and adolescents on the autism spectrum.[543] However, majority of the studies are limited by small sample sizes, high risk of bias and significant heterogeneity in regard to the type of intervention and how it is being delivered, hence resulting in low certainty of the reported results.

Despite the lack of evidence in this population, the benefits of physical activity in improving sensory-motor, cognitive and social skills and general well-being in all children are well-documented.[544–547] Thus, it is recommended that children and adolescents on the autism spectrum should engage in a variety of physical activities (with age-appropriate frequency and intensity) as outlined in the national Physical Activity Guidelines for children.[546,548] Children and adolescents on the autism spectrum who have difficulties engaging in physical activities because of a specific medical condition, sensory processing difficulties or social difficulties should consult the relevant professionals for individualised advice and recommendation.

R 6.38 ***Children and adolescents on the autism spectrum are recommended to engage in a variety of physical activities, at age-appropriate intensity and frequency, as indicated in the national physical activity guideline for children. [EM6-36]***

6.2.4.11 Animal-assisted Therapy

Animal-assisted interventions utilise interactions with animals to teach or support skill development.[549] Based on the current literature, a wide variety of animals is used in the studies examining the effects of animal-assisted interventions, with horses and dogs being the most frequently studied animals. In general, there is a lack of standardisation of intervention practices among studies investigating the effects of animal-assisted interventions. Most studies also employed non-RCT designs. Studies with more robust designs (i.e., RCT) showed inconsistent results across outcomes. Review papers examining the effects of different types of animal-assisted therapies generally concluded null or inconsistent effects of animal-assisted interventions on treating core symptoms of autism.[549–551]

The effects of canine-assisted and equine-assisted therapies were further examined. Inconsistent findings were reported among review studies and RCTs evaluating canine-assisted interventions.[551–553] For equine-assisted interventions, small positive effects were reported on social interaction and communication in one meta-analysis.[554] Positive effects on social communication were also reported in

the parent or teacher-rated social skill measures at the single study level.[555–557] However, the level of certainty of the positive effects was rated as low.

Overall, the current body of literature provides insufficient evidence to support the efficacy of animal-assisted interventions in reducing the core symptoms of autism and improving communication, social interaction, motor skills, and adaptive functions of children on the autism spectrum. Some emerging evidence suggests the efficacy of equine-assisted intervention. Further large-scale, high-quality studies will be needed to ascertain the intervention effect for children on the autism spectrum.

R 6.39 ***Animal-assisted interventions are not recommended as treatment for core symptoms of autism in children and adolescents. Further research is needed to establish potential treatment benefits. [EM6-37]***

6.2.4.12 Mindfulness

Mindfulness intervention refers to programmes with a focus on increasing mindfulness in participants. Mindfulness is defined as the ability to pay attention to the present moment in a non-judgemental and compassionate manner.[558,559] These interventions are usually conducted in a group and include both formal meditation practice and teachings on how to apply mindfulness in daily life.[558,559] The mindfulness interventions reviewed in this Clinical Practice Guidelines include the mindfulness-based stress reduction and mindfulness-based cognitive therapy program, with allowance for some modification for children and adolescents on the autism spectrum under 18 years old. The intervention has to be delivered by a trained professional.

There is insufficient evidence to support the recommendation for mindfulness intervention to improve core autism features and well-being in children and adolescents on the autism spectrum.[558,560] Most studies report very small to small treatment effect size for mindfulness intervention in children and adolescents on the autism spectrum.[558,561] There is only one study that reported moderate effect size in improvement in behavioural and emotional problems. However, certainty of evidence is very low, thus support for benefits cannot be established.[562]

While the evidence is not able to support a recommendation for mindfulness intervention for all children and adolescents on the autism spectrum, positive trends in general well-being and low harm potential could position mindfulness intervention as part of shared decision-making with parents or caregivers.[560,563] Progress monitoring and expected benefits should be discussed with caregivers.

R 6.40 ***Mindfulness intervention is not recommended as treatment for core symptoms of autism in children and adolescents. However, it may be considered for selected children and adolescents on the autism spectrum to improve general wellbeing. [EM6-38]***

6.2.4.13 Facilitated Communication

Facilitated communication (FC) is a technique that involves a person with a disability pointing to letters, pictures or objects on a keyboard or a communication board, typically with physical support from a ‘facilitator’. Proponents of FC claim that it reveals previously undetected literacy and communication skills in people with communication disability.

Systematic reviews of literature up to 2014 and between 2014 and 2018 reveal that there is no evidence that FC is a valid form of communication for individuals with severe communication disabilities.[564] There continues to be no evidence demonstrating that individuals with communication disabilities are authors of the messages generated by FC. It continues to be contested in high profile court cases, with many organisations worldwide issuing position statements against FC use.[565,566]

R 6.41 ***Facilitated communication should not be used in the treatment of children and adolescents on the autism spectrum, as there is no evidence of benefit. [EM6-39]***

Finally, there are four CAM therapies for which there is no new reliable or substantive research evidence in the past 10 years. These are:

1. Bioresonance
2. Wilbarger brushing protocol
3. Holding therapy
4. Patterning with/without masking.

Bioresonance therapies and other therapies that use electronic devices claim to both diagnose diseased internal organs and 'normalise' the body's electrical properties and wave emissions. This is based on an unproven idea that unhealthy cells or organs emit altered electromagnetic waves, and that changing these waves back to 'normal' will 'heal' the body.[567] A series of 2 papers involving bioresonance therapy is available – a small case series and a report on a longitudinal data from an ongoing autism intervention study.[568,569] The interventions include supplementation with sulforaphane and application of bioresonance therapy, with only five patients received bioresonance therapy.

Based on the available information, bioresonance therapy is not recommended as standard treatment for core symptoms of autism in children and adolescents, as there is insufficient evidence of benefit.

The latter three were included in the 2010 Autism CPG and the recommendations for these three therapies remain unchanged.

- Wilbarger brushing protocol is not recommended as treatment for core symptoms of autism in children and adolescents.
- Holding therapy should not be used in the treatment of children and adolescents on the autism spectrum as there is no evidence of benefit and significant potential for harm, including death.
- Patterning without masking is not recommended as treatment for core symptoms of autism in preschool children because there is no evidence of benefit.
- Patterning with masking should not be used in the treatment of children and adolescents on the autism spectrum as there is no evidence of benefit and there is potential for harm to the child's developing brain.

Abbreviations

AIT, auditory integration therapy; BCAAs, branched-chain amino acids; CAM, complementary and alternative medicine; CAMP, Children's Autism Metabolome Project; CARS, Childhood Autism Rating Scale; CoQ10, coenzyme Q10; CPG, clinical practice guidelines; DMG, dimethylglycine; DMT, dance/movement therapy; EEG, electroencephalography; FC, facilitated communication; GFCF, Gluten-free casein-free; GI, gastrointestinal; HBOT, hyperbaric oxygen therapy; IBD, inflammatory bowel disease; KD, ketogenic diet; MMR, measles, mumps, rubella; MTT, microbial transfer therapy; RCT, randomised controlled trial; ROS, reactive oxygen species; rtfMRI, real-time functional magnetic resonance imaging; SF, sulforaphane; tDCS, transcranial direct current stimulation; VNS, vagal nerve stimulation; WHO, World Health Organization.

CHAPTER 7: CO-OCCURRING CONDITIONS IN AUTISM

7.1 INTRODUCTION

The presence of a chronic condition that co-occurs, at the same time or in tandem, with a primary disease is a comorbidity.[570,571] Due to language sensitivity preferences, comorbidities will be referred to as co-occurring conditions wherever possible. Prior to the revision of the DSM as the 5th edition (DSM–5), there were challenges in making diagnoses for certain mental health conditions in individuals on the autism spectrum. With the DSM–5, dual and additional diagnoses can be made and therefore management will be impacted, with more pertinent information for treatment and prognosis.[570,571]

The prevalence of co-occurring conditions varies widely as autism is a spectrum condition with many varied pathophysiology and aetiologies.[572] Assessments for co-occurring conditions can thus be challenging and ascertainment can be difficult. A study of 42569 individuals on the autism spectrum and 11389 controls found that 74% of those on autism spectrum had at least one co-occurring condition.[573] In another study, about half of individuals on the autism spectrum were reported to have 4 or more co-existing conditions with only 4% not having any co-occurring condition.[570]

7.1.1 Implications of Co-occurring Conditions in Autism

Co-occurring conditions in autism should be considered when symptoms and signs of conditions are present, independent from the core diagnostic features of autism.[570] They often present in preschool years and predict maladaptive behaviours, independent of severity of core symptoms.

The presentation of each co-occurring condition may not be straightforward, as these may have multiple forms, or present in atypical ways that can be unrecognisable unless one has a high index of suspicion. Many factors confound the identification of a co-occurring condition in autism, such as communication difficulties, the ambiguity of symptoms, their variation from those in the general population, or their change over time.[574] Irregular behaviours and symptoms may be labelled to be 'just part of autism'.[574] Specifically, many children and adolescents on the autism spectrum have issues with communication. Majority of toddlers on the spectrum are unable to point to indicate their needs or interests.[570] For instance, head banging may result from headache or a pain that cannot be expressed. In addition, many older children in this population also have sensory processing issues, interoception difficulties (reduced awareness of internal body sensations), with difficulty interpreting their own sensations, or have atypical perception of discomfort or pain.[570,574] Changes in behaviour, even maladaptive behaviours, may indicate the presence of pathology, but can also mask autism itself and a co-occurring condition.[570]

Thus, both psychiatric and somatic conditions often complicate management as these may exacerbate or mitigate typical features of autism. Sometimes, the first presentation of autism can be a symptom or sign that is associated with a co-occurring condition. Co-occurring conditions, on their own, may imply worse outcomes and increased health needs.[571] Therefore, co-occurring conditions need to be identified when present as they can have detrimental effects on overall functioning and family life, often above the effects of the core symptoms of autism.[571] There are increased levels of morbidity and mortality, depression and reduced social well-being[570,574] associated with the presence of co-occurring conditions. Healthcare costs increase and stress levels (both in the individual and caregivers) invariably increase.[571] Treatment of co-occurring conditions would thus improve the overall quality of life.

7.1.2 Assessment for Co-occurring Conditions

It is important to screen for co-occurring conditions when children and adolescents on the autism spectrum attend review visits. This would also imply that all children and adolescents diagnosed with autism should have regular medical follow-up and be monitored for the occurrence of co-occurring conditions through their life span. Healthcare professionals should have a high index of suspicion for a co-occurring problem in a child or adolescent on the autism spectrum when:[570]

- signs and symptoms cannot be explained despite a thorough history taking and physical examination (including self-injurious and aggressive behaviours)
- maladaptive behaviours are present, which cannot be contextualised during psycho-educational behavioural assessments
- there are changes from baseline (e.g., skill regression especially after 3 years of age)
- the child or adolescent is not responding as expected to therapeutic interventions,
- there is a history of frequent visits to the emergency room, or
- there is a history of taking multiple over-the-counter drugs and dietary supplements.

Risk factors for co-occurring conditions in autism may include increasing age and male gender.[570]

One of the challenges in the detection of co-occurring conditions includes the limited availability of instruments designed to screen for co-occurring psychopathology. Some tools have been developed including Psychopathology in Autism Checklist and Autism Spectrum Disorder -Comorbidity for Adults.[575] In the younger age group, it is even more challenging to screen and diagnose for co-occurring conditions. One tool that has been psychometrically validated is the Baby & Infant for Children with aUtIsm Traits (BISCUIT), Part II.[576,577] It provides age-based cut-off for the presence of both features of autism and presence of co-occurring conditions. The Autism Spectrum Disorders Comorbidity-Child Version can also be considered.

It is important that all children and adolescents on the autism spectrum are monitored closely for co-occurring conditions through regular follow-up with a healthcare professional over their growing years. Early identification of co-occurring conditions will allow for earlier treatment, so as to reduce negative consequences. Co-occurring conditions may be somatic or psychiatric by classification, sometimes with educational and cognitive impact.

GPP 7.1 ***Children and adolescents on the autism spectrum should be followed up serially at spaced intervals in a holistic manner as they are at increased risk of academic, neuropsychological, adaptive challenges and certain medical conditions. Assessments and evaluations for these should be considered as needed when issues in these domains are identified. [EM7-1]***

7.2 NEURODEVELOPMENTAL CO-OCCURRING CONDITIONS IN AUTISM

7.2.1 Learning Difficulties

7.2.1.1 Introduction

Children and adolescents on the autism spectrum encounter learning difficulties in association with many inherent challenges including language impairment (see Section 7.2.5), intellectual disability (ID) (see Section 7.2.6), emotional health, executive function and memory amongst other factors.[578] Other co-occurring disorders, such as attention-deficit hyperactivity disorder (ADHD), also add to learning challenges for those on the autism spectrum.

Various studies have reported higher rates of specific learning disorder (SLD) among school-aged children on the autism spectrum.[579] About 30–60% of children on the autism spectrum have some difficulty in developing literacy skills, compared to 5-15% of neurotypical peers.[580] One of the most researched SLD is what was previously known as Dyslexia. DSM-5-TR redefines Dyslexia as an SLD with Impairment in Reading, characterised by problems with word reading accuracy, reading fluency, and reading comprehension that are not the result of sensory differences, neurological disorders, intellectual disabilities, or inadequate educational instruction. The prevalence of an SLD with Impairment in Reading in children on the autism spectrum ranges from 6 to 30%.[581] However, the reading difficulties observed in those on the autism spectrum are different from that of a child without autism, which is more characterised by phonological difficulties. It is likely that the reading difficulties in autism are mediated by language difficulties though this is not the sole contributor. A 2015 study reported that the genes for language impairment and SLD also contribute to language traits in children on the autism spectrum.[582]

7.2.1.2 *Implications of Learning Difficulties in Autism*

When a learning disorder is not addressed or remediated, the affected child may face significant challenges and may experience academic failure, with impact on their emotional health and sense of self-worth. Aside from social communication difficulties, children on the autism spectrum sometimes struggle in school academically given that their learning needs differ from their peers.

Some of the symptoms of autism, such as difficulties in expressing one's thoughts, might cause children on the autism spectrum to struggle as they are not able to communicate their needs effectively. These challenges can also impact the way in which they engage with their peers and teachers. Checking in on these children would be essential to understand their learning and social needs and better support them. Also, as children journey through the education system, academic and social demands increase, and they would require different supports and access arrangements as indicated.

7.2.1.3 *Assessments*

Prior to the start of primary school, some children on the autism spectrum may have a school readiness test to aid in school placement or put in place school supports, if needed. Children who are referred for suspected learning difficulties that cannot be accounted for by their diagnosis of autism should go through a holistic assessment to inform caregivers and educators of their needs profile so that intervention and education can be tailored to meet these children's needs. This may include a cognitive assessment followed by specific assessments (e.g., literacy or numeracy assessments, phonological assessments.

R 7.2 ***Children and adolescents on the autism spectrum presenting with academic challenges should be evaluated for their learning needs so as to guide parents and educators on further diagnostic assessments, interventions and support required, including access arrangements for learning. [EM7-1]***

7.2.2 *Impaired Adaptive Function*

7.2.2.1 *Introduction*

Adaptive skills refer to practical daily living skills required for independent living. Adaptive skills are strongly correlated to IQ in typically developing children. However, in children on the autism spectrum, significant delays in adaptive behaviour with adaptive scores falling one or two standard deviations below population mean have been reported, even in the absence of cognitive delays.[583–585] Adaptive skills also encompass feeding, toileting and other skills related to self-care. Delays in these can be due to multiple factors related to autism, including sensory hypersensitivity and communication difficulties. Such adaptive function difficulties can have profound impacts on caregiving and day-to-day life of the individual.

7.2.2.2 *Adaptive Skills and Their Association with Cognition and Autism Symptoms*

Interestingly, cognition contributes to the variance in adaptive skills among children on the autism spectrum.[584,586,587] Yang et al. (2016), in their study of 77 young autistic children, reported that children with higher IQ showed significant lower adaptive skills than their cognitive skills would predict, while those with lower IQ showed higher adaptive skills than their cognitive skills would predict.[584] There is also some evidence to suggest that as children on the autism spectrum grow and make gains in IQ, they fail to achieve corresponding gains in adaptive skills, resulting in a higher discrepancy between IQ and adaptive skills in older children and adolescents.[585,588,589] Poor association between autism symptoms and adaptive skills have also been reported in some studies.[583,584,590]

7.2.2.3 *Assessments*

Adaptive function assessments can include parental reports and clinical observations. Some of the commonly used standardised assessments include the Adaptive Behavior Assessment System (ABAS-3), Vineland Adaptive Behavior Scales (VABS), Pediatric Evaluation of Disability Inventory (PEDI), Functional Independent Measure (WeeFIM), Canadian Occupation Performance Model (COPM) and

Assessment of Motor Process Skills (AMPS/ School AMPS). Adaptive function should be assessed and serially tracked to support the functional needs of the child as indicated.[591]

R 7.3 ***Professionals should be aware that children and adolescents on the autism spectrum may have significant delays in adaptive skills even in the absence of cognitive delays. Adaptive function should be assessed and monitored to support the functional needs of the child as indicated using standardised measures. [EM 7-2]***

7.2.3 Attention-Deficit Hyperactivity Disorder

7.2.3.1 *Introduction*

The prevalence rate of children diagnosed with both attention-deficit hyperactivity disorder (ADHD) and autism ranges from 40–70%.[592] The initial age at which symptoms of hyperactivity are observable in children on the autism spectrum ranges from 12–39 months.[571] On average, children received a dual diagnosis of autism and ADHD at around 6 years old.[593] As autism and ADHD are both neurodevelopmental disorders and have a high joint prevalence rate, it has been suggested for children on the autism spectrum to be screened for ADHD between the ages of 4–5 years old.

7.2.3.2 *Implications of ADHD in Autism*

Research has also shown that children on the autism spectrum with normal cognition tend to be misdiagnosed as having ADHD alone,[594,595] suggesting that children diagnosed with ADHD should also be screened for autism. Hence, although early identification is key, there may be no fixed age where children on the autism spectrum should be screened for ADHD, as symptoms might manifest later than the recommended age of screening. It is therefore important for healthcare professionals to look out for common overlapping symptoms of autism and ADHD.

7.2.3.3 *Assessments*

Prior to the publication of the DSM-5, a diagnosis of ADHD and autism could not be made simultaneously. Hence, assessment tools that screen for ADHD tend to be for the general population. Some of the more commonly used tools in Singapore include Conners Comprehensive Behavior Rating Scale (CBRS), intended for ages 6 to 18; National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale, intended for ages 6 to 12; and Child Behavior Checklist (CBCL), created for ages 6 to 18.

Given the overlaps in diagnostic symptoms between ADHD amongst children on the autism spectrum and the difficulty in assessing for ADHD amongst these children (especially so for children who might be non-verbal or have other co-occurring developmental disorders), it is essential for healthcare professionals to screen for ADHD routinely during developmental review visits.

R 7.4 ***Professionals should be aware of the higher incidence of attention-deficit hyperactivity disorder (ADHD) among children and adolescents on the autism spectrum. In the presence of symptoms of ADHD, especially after the age of 5, prompt screening and referral for a thorough diagnostic evaluation using validated measures should be made to facilitate early management. [EM 7-3]***

7.2.4 Development Coordination Disorder

7.2.4.1 *Introduction*

Developmental Coordination Disorder (DCD) is a condition affecting motor coordination and motor planning. Children with DCD appear clumsy and disorganised, and these difficulties interfere significantly with their activities of daily living.[86,596] In addition to motor clumsiness, recent studies have also shown that children with DCD have significant difficulties with executive function[597,598] and are at increased risk of social participation challenges and complex behavioural and psychosocial issues.[599,600]

As a result of the changes in DSM-5 in 2013, autism and DCD can now be diagnosed simultaneously in individuals.[86] It is estimated that up to 90% of children on the autism spectrum experience significant motor difficulties.[601–603] Results from two recent meta-analyses have reported substantial overall difficulties, with large effect sizes (g=1.22 and 1.04 respectively), across both gross and fine motor skills in children on the autism spectrum compared to typically developing children.[604,605]

7.2.4.2 *Implications of DCD in Autism*

Despite the high prevalence of motor difficulties in children on the autism spectrum,[604,605] dual diagnoses of autism and DCD are seldom made in practice due to the difficulties in determining whether the motor difficulties are related to DCD or to autism alone.[606] In a large study of 11814 children on the autism spectrum, Bhat (2020) reported that 86.9% of the children on the spectrum were at risk for DCD but only 15.1% held a dual diagnosis of autism and DCD.[607] More research is needed to develop a clear guideline to determine when the motor difficulties are beyond what is expected of autism.[606,608] Due to the challenge in diagnosing DCD in children on the autism spectrum, this condition continues to be under-recognised and under-diagnosed.[606] This type of misdiagnosis may prevent access to treatment and educational/vocational support required during the school years and beyond.[606,608]

7.2.4.3 *Assessments*

It is important to monitor the motor development of children on the autism spectrum, track motor milestones, gross and fine motor skills as well as motor planning and organisation. Formal screening and diagnosis of DCD should be conducted in those with persistent motor challenges, especially beyond the preschool years.

Screening tools for DCD include Little Developmental Coordination Disorder Questionnaire (3–4-year-old children), Developmental Coordination Disorder Questionnaire (5–15 year old children) and Movement ABC motor checklist (5–12-year-old children). Children who are identified to be at risk for DCD should be referred for expert assessment. It is recommended that a multidisciplinary team is involved in the evaluation, which should include parental report, family and sensorimotor history, clinical observation and standardised testing.

Both Movement ABC-2 and Bruininks-Oseretsky Test of Motor Proficiency-2 are the recommended criterion measures for assessing motor difficulties when DCD is suspected.[609–611] Formal diagnosis is recommended only for children age 5 and above, while diagnosis below 5 years old is made only in cases of severe symptoms.[609] The 16th percentile for the total score in either measure should be used as a cut-off. If a child scores ≤ 5th percentile in one domain but >16th percentile in other domains, a DCD diagnosis can be made if other DSM-5-TR criteria are met.[609] Cognitive, social and language differences in children on the autism spectrum might affect motor skills assessment. To ensure an accurate motor assessment, the assessor needs to be mindful of the environment in which the assessment take place and how the instructions are given.[612]

R 7.5 ***Professionals should be aware that children and adolescents on the autism spectrum are also likely to have motor difficulties. Formal screening for and diagnosis of Developmental Coordination Disorder (DCD), using validated measures, should be undertaken in those with ongoing concerns for motor coordination and organizational skills beyond the preschool period. [EM 7-4]***

7.2.5 Language Disorder/Impairment

7.2.5.1 *Introduction*

Language disorder is a neurodevelopmental disorder characterised by difficulties in the learning and use of language across the various modalities of speaking, writing and sign language. Language abilities can be considered in terms of receptive and expressive skills, with receptive skills referring to the ability to understand language, and expressive skills referring to the ability to produce language. It is important to assess both receptive and expressive skills as an individual can present with different severity of difficulties in each. Most research, however, reports only on expressive or functional

language abilities in children on the autism spectrum. About 30% of children who were minimally verbal at 4 years old, continued to have limited language by 8 years old (*N*=535).[613] It is estimated that about a third of individuals on the autism spectrum continue to be minimally verbal throughout their lifetime.[614,615]

7.2.5.2 *Implications*

Children on the autism spectrum can also have varying levels of language abilities that range from below average to above average, when compared to other children of their age. Their language abilities can have a significant impact on their ability to function in everyday life, and to learn and complete age-appropriate academic tasks.[614] Due to the highly verbal nature of our national mainstream curriculum, and how the curriculum is conducted in mainstream schools, language impairment can have a significant impact on an autistic child's coping in mainstream school.

7.2.5.3 *Assessments*

Language delay can be identified in children as young as 1 to 2 years old. Language delay is often a presenting feature of autism and/or ID. A clear differential diagnosis of ID versus language impairment may not be possible until the child is 5 to 6 years old, using standardised assessments for intellectual abilities. A separate diagnosis of language impairment is not necessary in children with intellectual impairment unless the language challenges are clearly not accounted for by the intellectual difficulties. Even though the DSM-5-TR and ICD-10 show a greater emphasis on expressive, verbal or functional language skills when describing the language abilities of a child on the autism spectrum, it is also important to assess a child's receptive language skills. It is known that children on the autism spectrum often show greater weaknesses in their receptive language skills compared to their expressive language skills, hence evaluating their receptive language skills will help inform their intervention and educational needs.

R 7.6 ***Professionals should be aware of the need to assess for language, learning and other co-occurring developmental disorders in children and adolescents on the autism spectrum and support them accordingly. Caregivers would benefit from counselling regarding these co-occurring conditions and their potential impact on their child's learning and adaptive behaviour. [EM 7-5]***

7.2.6 Intellectual Disability (ID)

7.2.6.1 *Introduction*

Intellectual disability is a neurodevelopmental disorder characterised by deficits in both intellectual and adaptive behaviour functioning with an onset during the developmental period.[86] ID is more reliably diagnosed from 5–6 years old. Estimates of rates of ID in the autism population have been varied and dependent on the population sampled.[17] The NICE Guidelines UK (2011) estimated a pooled prevalence rate of 65% from studies up till 2010.[14] Surveillance data from the United States (*N*=3390) found that 31.6% of autistic individuals met criteria for a diagnosis of ID (i.e., IQ score ≤70), with 24.5% having IQ scores in the borderline range (i.e., 71 to 85) and 43.9% having average or above average intellectual abilities.[616]

7.2.6.2 *Implications*

The intellectual abilities of children on the autism spectrum can have as significant an impact as their core symptoms of autism on their ability to function in their everyday lives, and to learn and complete age-appropriate academic tasks. A concurrent diagnosis of ID has significant implications for educational planning for children on the autism spectrum in Singapore. Not having a concurrent ID, and having functional phrase speech by 4 years old, have been found to be strong predictors of better outcomes in adults on the autism spectrum.[614] Therefore, understanding the intellectual and language profile of a child on the autism spectrum can provide caregivers with a clearer picture of their child's strengths and needs, and help them understand the need for specialised interventions or educational provisions (i.e., special school placements).

7.2.6.3 *Assessments*

As children on the autism spectrum have differing needs and areas which require intervention or monitoring, cognitive testing may be recommended as part of a comprehensive evaluation to assess their overall cognitive abilities and inform treatment and educational planning (if needed). The specific timing and type of cognitive test used will depend on the child's individual needs. (See Education Chapter 5, section 5.3.2)

Children on the autism spectrum often present with an uneven intellectual profile. Hence, separate measures of the child's verbal and nonverbal are often more representative of the child's intellectual profile. It can be challenging to engage 5-6-year-old children on the autism spectrum who are likely to have moderate to severe ID to complete standardised cognitive assessments (e.g., Weschler, Stanford-Binet, and Singapore Ability Scales), due to their social communication and behaviour difficulties. A diagnosis of ID can be made in the absence of standardised scores, as per recommended guidelines on the assessment of severity of ID in the ICD-11 and in previous editions of the DSM. The individual's adaptive functioning should be considered, using clinical judgement and behaviour indicators based on the DSM-5-TR or ICD-11 diagnostic criteria for ID.

Children diagnosed with autism and/or ID may have been diagnosed with global developmental delay (GDD) when they were <5 years old. GDD is a term reserved for children below the age of 5 years, and describes significant delays in two or more domains of development.[5] The NICE Guidelines UK (2017) recommends considering whether a child with autism has coexisting GDD or ID.[14] A diagnosis of GDD should be reassessed for a child with autism at 5–6 years old.

R 7.7 ***Children on the autism spectrum who have global developmental delay should be evaluated towards the end of the child's preschool period for the presence of intellectual disability. The diagnosis of global developmental delay should not be used when the child is past 5 years of age. [EM 7-6]***

7.2.7 Sensory Processing Difficulties

7.2.7.1 Introduction

Sensory processing difficulties (SPD) can be broadly classified into 2 categories: 1) sensory modulation difficulties characterized by hyper- or hypo-responsiveness to sensory inputs and 2) sensory integration difficulties which include difficulties in postural control, bilateral integration, body-centered praxis and visuopraxis.[226,617] It is estimated that the prevalence of SPD in children on the autism spectrum ranges from 60–97%, with difficulties reported across all ages and autism severity.[618–621]

Acknowledging the high prevalence of SPD in children on the autism spectrum, the DSM-5-TR has included 'hyper- or hypoactivity to sensory inputs' as one of the four items in Section B of the ASD diagnostic criteria.[86]

7.2.7.2 *Impact of SPD on Autism*

While earlier research has often viewed sensory processing difficulties and social communication difficulties independently, new theoretical and empirical evidence has suggested a much stronger relationship.[622–625] Robertson & Baron-Cohen (2017), in their review of sensory perceptions in autism, concluded that sensory symptoms are a core characteristic in the neurobiology of autism. They posited that sensory processing differences during early development are predictive of diagnostic status and social communication difficulties later in childhood. They further suggested that research on sensory symptoms might shed light on how motor behaviour, emotion, communication and cognition might be related and provide direction for translational research.[624]

7.2.7.3 *Assessment*

Children who are suspected to have sensory processing difficulties should be referred to appropriately trained specialists with relevant expertise for assessment. If screening is required, Sensory Processing Measure or Sensory Profile can be used. Other validated assessment tools include Evaluation in Ayres

Sensory Integration and Sensory Integration and Praxis Tests.[626–628] Multiple method of assessments including questionnaires, observation and validated assessments are recommended for a comprehensive assessment.[629] It is important that appropriately trained professionals administer such assessments.

R 7.8 ***Children and adolescents on the autism spectrum with concerns for sensory processing difficulties, should be assessed via multiple modes of assessment including questionnaires, direct observations, and validated assessments, by an appropriately- trained individual, to facilitate a comprehensive evaluation. [EM 7-7]***

7.3 MENTAL HEALTH CONDITIONS IN AUTISM

7.3.1 Introduction

The diagnosis of mental health disorders in autism has become better recognised and more relevant in recent years[630] with the DSM-5-TR[86] no longer limiting the dual diagnoses of psychiatric conditions in autism. Recent studies have reported that 36.84% of children on the autism spectrum had at least one psychiatric diagnosis – of which, 17.16% had only one psychiatric condition, 9.87% had two, and 10.21% had more than three.[631–634] However, there exist differences in reported prevalence of specific mental health conditions across different populations. The specific pooled prevalence rates of common mental health conditions from the NICE128 guidelines are as follows: Anxiety disorder 27% (range 1.47–62.0%),[635–639] oppositional defiant disorder 23% (range 12.0–48.0%),[635–637] Tourette's syndrome and tic disorder 19.0% (range 12–19.0%),[635,637,640–642] obsessive compulsive disorders 8% (range 9.0–22.0%),[635–637] depressive disorders 9% (range 2.5–47.1%),[635–638] bipolar disorders 5% (range 5–21.4%),[634,643] schizophrenia (including psychosis and affective disorders 4% (range 4–6.7%)[634,643–647] and eating disorders 4.7% (range 1.4–7.9%).[643,648,649]

7.3.2 Implications of Mental Health Disorders in Autism: Considerations in Diagnosis

Diagnosis of mental health disorders in autism can be challenging. While symptoms may sometimes clearly reflect co-occurring conditions, there may be scenarios whereby presentations are more complex. Mental health conditions often have atypical presentations in children and adolescents on the autism spectrum. "Diagnostic overshadowing", whereby psychiatric symptoms may be mistakenly taken as part of autism, may lead to overlooking mental health conditions in persons on the autism spectrum.[650–653] Conversely, autism symptomatology may sometimes be misunderstood to be mental health issues, such as social avoidance in autism appearing to be like Social Anxiety,[654] possibly leading to a missed autism diagnosis. Assessment of mental health issues may be further complicated in children and adolescents on the autism spectrum with ID or communication difficulties with limited insight or difficulty communicating their symptoms. These individuals are often overlooked as professionals and researchers focus on those with better cognitive abilities.[655–657]

The presence of co-occurring conditions significantly decreases quality of life; accentuates problems like restlessness, passivity, social isolation, aggressiveness, irritability and self-injury; worsens long term outcomes; and increases the risk of mortality.[658–660] Hence, it is recommended that appropriate assessment be conducted when a co-existing mental health condition is suspected for children and adolescents on the autism spectrum. Healthcare professionals should be familiar with and able to recognise these co-occurring conditions in children and adolescents on the autism spectrum and provide or refer these children to appropriate services for assessments.[661] While there is insufficient evidence to conduct routine assessments for these co-occurring conditions, detailed assessments of these issues should be conducted when clinically indicated.[662] Management of these specific mental health conditions may sometimes have to be tailored and adjusted in children and adolescents on the autism spectrum, as opposed to standard treatment approaches in the general population (see Chapters 3 and 4 on Intervention and Pharmacological Treatment).

R 7.9 ***Children and adolescents on the autism spectrum presenting with mental health symptoms (e.g., depression, anxiety) that impact on their daily functioning should be***

referred for further evaluation. Professionals should therefore have a high index of suspicion and be trained to look for co-occurring mental health issues in this group of individuals. [EM 7-8]

7.4 GENDER VARIANCE AND DYSPHORIA

7.4.1 Introduction

Gender dysphoria, a diagnostic term from the DSM-5-TR, is used to define individuals with an incongruence between assigned and experienced gender.[86] This could include a diversity of gender identities including transgender, non-binary, genderfluid, agender, genderqueer, two-spirit, bigender or others.[663] Based on current recommended practice, the collective term often used is 'transgender and gender diverse'. There often could be an association of distress of one's own biological sexual characteristics and assigned social gender role, due to a strong and persistent cross-gender identification.[664] Therefore, gender variance is not the pathology whereas dysphoria is from the distress that is caused by the mind and body not being aligned and/or societal marginalisation of gender-variant people.[86] In the general population, 0.4–1.3% is estimated to be transgender and gender diverse.

Several studies have suggested a greater proportion of gender variance among individuals on the autism spectrum, with estimates ranging from 4.7–5.4% and up to a 7.76 fold increase in likelihood of gender variance amongst those on the autism spectrum as compared to controls.[664–666] Children on the autism spectrum were over 4 times as likely to be diagnosed with a gender dysphoric condition in a large study of 48672 children.[667]

Conversely, there is also an increased rate of diagnosis of autism amongst those with gender variance. Studies reported 7.8–13.8% meeting diagnostic criteria for or having a prior diagnosis of autism amongst children and adolescents referred to gender clinics.[663,665,668]

7.4.2 Implications of Gender Variance and Dysphoria in Autism

Co-occurring mental health conditions are significantly higher by prevalence in those with gender dysphoria, diversity or incongruency, with higher risk of self-harm or suicidal tendencies.[668] It is reported that gender dysphoria started before puberty in 24% of adolescents on the autism spectrum compared to 4% in controls.[669] There was more self-harm/suicidality and psychotic symptoms in these individuals as well. In addition, those with these co-occurring disorders suffered from social isolation and had fewer love and sexual experiences than adolescents without autism.[669]

7.4.3 Assessments

Guidelines exist for the assessment of transgender and gender nonconforming (TGNC) individuals, with the essential need for psychological assessment, as per the World Professional Organization for Transgender Health (WPATH)'s *Standards of Care, Version 7* and American Psychological Association.[670] The DSM-5-TR serves as the guide in applying the criteria for gender dysphoria. The International Classification of Disease-10 is an alternative diagnostic guide. Mental health also needs to be explored thoroughly with a qualified mental healthcare professional.

A guide to the approach for further evaluation and management has been provided by the American Psychiatric Association Workgroup on Treatment of Gender Dysphoria.[671]

GPP 7.10 ***Professionals should be aware of the association between gender variance and autism. Children and adolescents on the autism spectrum who present with gender variance issues (where gender variance is an umbrella term used to describe gender identity, expression, or behaviour that falls outside of culturally-defined norms associated with a specific gender) may need further referral for evaluation and support for their social-emotional needs. [EM7-9]***

7.5 MEDICAL DISORDERS

The large, combined body of evidence indicating the high frequency of co-occurring conditions in autism means that every child and adolescent on the autism spectrum should have follow-up over time with a healthcare professional to monitor for medical conditions that may appear later in the timeline. It is important that every co-occurring condition is picked up and appropriate treatment instituted.

7.5.1 Epilepsy

7.5.1.1 *Introduction*

Autism has been associated with many neurological conditions, amongst which epilepsy has been widely studied. Epilepsy is a neurological condition characterised by episodic, unpredictable changes in mental status with recurrent seizures or convulsions. The prevalence of epilepsy in individuals on the autism spectrum varies widely, with rates as high as 30–50%.[574,672,673] Up to 60% of children on the autism spectrum have abnormal electroencephalography (EEG), compared with 6–7% in normal children, and 10–30% of children on the autism spectrum have epilepsy.[674] The prevalence for epilepsy in children on the autism spectrum aged 3–11 years was reported as 2.8% and adolescents on the autism spectrum aged 12–17 years as 4.1%.[572]

Risk factors for epilepsy in autism include ID, motor delays, syndromic features, and seizure onset either early in life (before 5 years of age) or in adolescence.[674] In different meta-analyses, the pooled prevalence of epilepsy was 21.5–23.7% in individuals on the autism spectrum with ID and 8–8.9% in those without ID.[574] Age was also a contributory factor, with a prevalence rate of 12.5% in children aged 2–17 years and 26% in those aged 13 and older.[574]

7.5.1.2 *Implications of Epilepsy in Autism*

The presence of epilepsy impacts heavily on a child or adolescent on the autism spectrum. This would include a variety of health concerns including further cognitive impairment and risk to life with prolonged seizures, recurrent hospitalizations, further investigations, missed school days and other social concerns.

See Chapter 2, Section 2.4.2 on Aetiology and Investigations for more details.

GPP 2.13 ***Electroencephalography (EEG) may be performed in selected children on the autism spectrum who develop clinical seizures, seizure-like movements and/or regression of developmental milestones. [EM2-8]***

7.5.2 Feeding Challenges in Autism

7.5.2.1 Introduction

Feeding is used to denote the process of food and drink ingestion in social environments where this would be considered the norm. Ingestion of food and drink is part of daily living skills, with some reports indicating 46 to 90% of children on the autism spectrum having feeding problems.[675,676]

Regulatory problems of feeding, sleeping, and excessive crying before the age of 2 have been found to be predictive of autism in preschool age[677] and predictive of dysregulated behaviour including negative emotions, conduct problems and hyperactivity in preschool and school age.[678] Early life eating habits were also found to be related to features of autism in childhood.[679]

Atypical eating behaviours were five times more common in adolescents on the autism spectrum than children with other developmental disorders and 15 times more common in autism than neurotypical kids.[676] This included selective intake, more ritualistic and/or idiosyncratic eating behaviours, pica (an eating disorder where one compulsively eats non-nutritive things that are not food), and neophobia (fear of new foods). These conditions may be separate from features of autism and the role of caregivers and other adults is important in the management. Nonetheless, no common individual characteristics were identified for adolescents on the autism spectrum who experience feeding or eating problems.[676]

Eating, sleeping, and excessive crying problems in infancy are often referred to as regulatory problems (RPs), with persistent RPs defined as being at a level regarded as being serious by a caregiver and/or professional beyond 3 months of age. Infant RP's have been negatively associated with later features of autism.[680–683] Persistent early RPs in those on the autism spectrum were also associated with later occurrence of a feeding disorder.[684]

7.5.2.2 Implication of Feeding Issues in Autism

Feeding issues in children and adolescents on the autism spectrum are multi-factorial in origin and could be related to differences in expressive and communicative abilities, social and cognitive skills, global processing, flexibility of thinking, communication and interpersonal functioning and social interactions.[675,676] The presence of feeding disorders can be a significant source of concern for parents. In particular, associations were significant between oro-motor, gastrointestinal and sensory problems amongst those on the autism spectrum.

The presence of feeding issues in children would raise concerns of growth and health as well as nutritional deficiencies; while in adolescents, it will raise concerns about weight, shape and body image.[676] Up to 86% of studies showed feeding disorders to be related to selective intake. In 2013, the diagnosis Avoidant/Restrictive Food Intake Disorder (ARFID)– a persistent, extreme version of picky eating, avoidant/restrictive food intake disorder – was introduced into the DSM- 5.[684] The prevalence of ARFID in preschool children on the autism spectrum is high (28%).

There have been many ways of classifying these feeding disorders, defined as when the child does not regulate his feeding as per his sense of hunger or fullness. A simple classification would involve:[675]

- Lack of interest in feeding (infantile anorexia)
- Sensory food aversions/selective food refusal: when the individual eats what meets their fixed preferences
- Gastrointestinal insults from past experiences: periods of longer than a week of tube-feeding put the child at risk for 'oral deprivation'.
- Current medical conditions such as allergies, reflux or other chronic illness interfering with feeding
- Persistent regulatory problems from infancy
- Caregiver-related issues.

Dovey et al. (2009) described an additional category, coined as 'autism-based food refusal', where children on the autism spectrum and feeding problems have 'seemingly illogical rules around what constitutes an acceptable meal', with no studies having examined the rationale for this state.[685] Selective intake was seen in 86% of children on the autism spectrum, with sensory sensitivities such as food textures being the primary reason for refusal in the majority.[676]

7.5.2.3 Assessment tools

The following have all been used for assessment of feeding and feeding behaviours:[675] Children's Eating Behavior Inventory (CEBI-R), Brief Autism Mealtime Behavior Inventory (BAMBI), Behavioural Pediatric Feeding Assessment Scale (BPFAS), Parent Mealtime Action Scale (PMAS), Feeding Demands Questionnaire, About Your Child's Eating (AYCE) and Eating Profile. Nutritional assessments using the Youth/Adolescent Questionnaire (YAQ) and examining food records can also be done. Direct Observations and using the Multidisciplinary Feeding Profile (MFP) and Schedule of Oral-Motor Assessment (SOMA) can also be used.

R 7.11 ***Professionals should be aware of an increased prevalence of feeding and eating disorders among children and adolescents on the autism spectrum. These may be related to multiple factors including feeding dysfunction, sensory sensitivity, adaptive delays, behavioural issues and cognitive difficulties as well as pica (eating of non-food items), rumination (the process of regurgitating and re-chewing previously swallowed foods), obesity and food neophobia (fear of new foods) which should be evaluated for, as necessary. [EM7-10]***

GPP 7.12 ***Children who are on the autism spectrum and have a history of persistent early-onset regulatory problems (defined as persistent problems with eating, sleeping and excessive crying beyond 3 months of age) may have a higher risk for feeding disorders and should be monitored for feeding and eating disorders. [EM7-10]***

7.5.3 Gastrointestinal Disorders

7.5.3.1 Introduction

There is a large variation between the rates of gastrointestinal (GI) symptom prevalence reported by individual studies. Children on the autism spectrum have been found to be significantly more likely to experience GI symptoms than children with typical development, with a prevalence of 9–91%.[686] Several studies have also demonstrated higher prevalence of GI concerns in children on the autism spectrum.[179,687–692] Current data may represent an under-estimate of GI symptoms and disorders because behaviours that are reflective of GI symptoms (aggression, disruptive behaviours, self-injury) may be interpreted as features of autism and therefore go un-investigated. Several studies report that GI symptoms experienced by children on the autism spectrum were two- to eight-fold elevated.[693–696] Presence of GI symptoms were reported more commonly in girls[695,697–700] but were unrelated to autism severity.[695,699,700]

7.5.3.2 Implication of Gastrointestinal Disorders in Autism

GI conditions that occur in children on the autism spectrum do not necessarily differ from typically developing children. These include upper GI tract conditions including reflux (5.5% estimated prevalence),[701] nausea (23.2–27.9%),[693,698] and vomiting (4.2–11.4%).[694,700] Lower GI tract conditions include constipation (22.1–65%),[693,694,696,697,700,702] diarrhoea (10.6–64.7%)[693,694,696,697,700] and pain on stooling (7.4–29.5%).[697,700] Generalised discomfort with abdominal pain and bloating (22.9–53.7%) can also occur.[689,693–696,700,703]

The increased prevalence of GI disorders in children on the autism spectrum and the difficulty in identification of the condition can make GI conditions a challenge for caregivers to diagnose and manage.

Children and adolescents on the autism spectrum who have GI symptoms are at risk for problem behaviours.[696,697,704–708] Specific behaviour problems proposed as possible expressions of GI distress include: abnormalities in sleep, stereotyped and repetitive motor mannerisms, self-injurious behaviour, abnormal eating habits, abnormalities in mood or affect, argumentative, oppositional, defiant, or destructive behaviours, aggression, temper tantrums and inappropriate speech.

When patients with GI disorders present with behavioural manifestations, the diagnostic evaluation can be complex. Healthcare professionals should consider that sudden and unexplained behavioural change can indicate underlying pain or discomfort and may signify a GI disorder. Behavioural treatment may be initiated while the concurrent medical illness is being investigated, diagnosed (or excluded), and treated, but the behavioural treatment should not substitute for medical investigation.[709]

7.5.3.3 Assessments

Growth, nutrition and dental hygiene should be reviewed on a regular basis in children and adolescents on the autism spectrum. Some children on the autism spectrum are at risk of encountering nutritional issues due to being on special restrictive diets due to perceived allergies or in an attempt to improve behaviour, the commonest being a gluten-free casein-free diet.[389,392,710–713] Healthcare professionals should be alert to potential nutritional problems in children on the autism spectrum. Evaluation by trained professionals who are familiar with nutrition support is recommended if caregivers raise concern about the child's diet or if the child exhibits selectivity of intake or is on a restricted diet.

Primary care nutritional assessment for each child and adolescent on the autism spectrum should include (1) weight for height or body mass index, (2) weight for age, (3) height for age, and (3) any marked changes in growth rate (percentiles over time).

Healthcare professionals should screen for sensory feeding issues which can limit intake and dental issues that may result in feeding difficulties. There is also an increased risk of obesity in this group of children with selective intake (see below).

Children and adolescents on the autism spectrum who present with GI symptoms warrant a thorough evaluation. Evidence-based algorithms for the assessment of abdominal pain, constipation, chronic diarrhoea, and gastroesophageal reflux disease (GERD) should be used. The American Academy of Paediatrics has issued a Consensus Statement on Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report as well as Recommendations for Evaluation and Treatment of Common Gastrointestinal Problems in Children With ASD.[709]

Awareness of the uniqueness of presentation of GI issues, education of caregivers and medical professionals will help in early identification of GI disorders, nutritional and feeding issues. This will potentially improve behavioural symptoms and may avoid severe medical problems in children and adolescents on the autism spectrum.

R 7.13 ***Healthcare professionals should be aware that children and adolescents on the autism spectrum have a higher occurrence of gastrointestinal conditions. Referrals for thorough evaluation should be made for those who present with persistent or recurrent gastrointestinal symptoms, such as colic or recurrent abdominal pain, vomiting, nonspecific diarrhoea, or constipation. [EM7-11]***

GPP 7.14 ***Healthcare professionals should be aware that children and adolescents on the autism spectrum, with gastrointestinal disorders may present with atypical behavioural issues that may be indicative of acute abdominal conditions. Evaluation for the presence of a gastrointestinal disorder should be considered for children and adolescents on the autism spectrum who present with unexplained, persistent or sudden-onset atypical behavioural symptoms (such as head banging or increased stimulatory behaviours). [EM7-11]***

GPP 7.15 ***Healthcare professionals should be alert to potential nutritional problems in children and adolescents on the autism spectrum. They should be monitored for their growth and nutritional status, in view of increased risk of metabolic and psychosocial complications related to being over or under weight. Referrals should be made as needed in the presence of poor growth or obesity. [EM7-11]***

7.5.4 Genetic Disorders

Several genetic disorders are associated with autism. This includes Fragile X syndrome, neurofibromatosis type I, tuberous sclerosis complex, Down syndrome, and Duchenne muscular dystrophy, with Fragile X syndrome (2–3%) being the most common single gene disorder in autism.[574]

A consideration for a co-existing genetic condition should be made for any child diagnosed with autism. Referral to a genetic specialist should be considered for further evaluation in the presence of markers indicating a possible genetic diagnosis (See Chapter 2: Aetiology and Investigations, Sections 2.1 and 2.4 for a detailed discussion on the genetic aetiology and role of genetic investigations in autism).

GPP 2.1 ***Healthcare professionals should be aware of the strong genetic heritability of autism and monitor for features of autism in children who have siblings and/or first-degree relatives on the autism spectrum. [EM2-1]***

GPP 2.2 ***Healthcare professionals should be aware that some genetic conditions or syndromes may be associated with autism and should monitor the affected child for features of autism. Examples of genetic conditions or syndromes include Fragile X syndrome, Angelman syndrome, Tuberous Sclerosis, Rett syndrome, PTEN Hamartoma syndrome and Down syndrome. [EM2-1]***

GPP 2.10 ***Children who present with autism and have additional clinical features suggestive of an underlying genetic condition (such as microcephaly, seizures, dysmorphic features, congenital anomalies or a positive family history of developmental disability) should be referred to a genetic specialist for diagnostic confirmation and counselling. Examples of genetic conditions or syndromes include Fragile X syndrome, Angelman syndrome, Tuberous Sclerosis, Rett syndrome, PTEN Hamartoma syndrome and Down syndrome. [EM2-1]***

GPP 2.11 ***Children who are diagnosed with autism may benefit from genetic testing which can be offered by healthcare professionals. Discussion on the exact genetic test(s) to consider should be conducted by a genetic specialist or similarly-trained professional. [EM2-1]***

7.5.5 Hearing Disorders

7.5.5.1 *Introduction*

The available data on the prevalence of hearing impairment amongst children and adolescents on the autism spectrum has not been conclusive.[714] It has been difficult to collate as the presence of one often confounds the diagnostic process for the other. Furthermore, audiological assessments can be difficult to conduct in these children. A recent study showed that the prevalence of hearing impairment ranged from 0% to 4.9% in children on the autism spectrum, with deafness or partial hearing loss observed in 2.9% in this group versus 0.5% in the general population for those aged 0–15 years and 3.9% amongst adolescents on the autism spectrum versus 0.8% for those aged 16–24 years.[572]

Conversely, there is strong evidence to indicate an association between autism and hearing impairment. Studies have shown a relative risk of autism in those with hearing impairment to be 14 times, with 2.2–9% of children with hearing impairment having a diagnosis of autism.[715,716]

Hyper-responsiveness may also be present in children on the autism spectrum. This is the pattern of exaggerated behavioural reactions to sensory stimuli, often displayed by children on the autism spectrum, and includes hyperacusis, hypersensitivity, sensory defensiveness, sensory modulation dysfunction, aversion, avoidance, hyperarousal and lack of habituation to sensory stimuli.[714] A study has shown that the presence of sound sensitivity in at least one ear was higher for children on the autism spectrum (37%) compared to typically developing peers (0%) and general population (estimates 8–15%). In this study, an abnormal finding on at least one measure of audiological functioning was 55% in the cohort on the autism spectrum compared to 6% of the typically developing peers (population estimates 14.9% for aged 6–19 years).[717]

7.5.5.2 *Implications of Hearing Disorders in Autism*

In individuals on the autism spectrum, hearing impairment exacerbates innate barriers for communication, increases struggle to use gestures for communication and intensifies social isolation.[718]

7.5.5.3 *Assessments*

Assessments for the presence of hearing impairment include a test battery approach for audiological assessments with objective tests to verify behavioural audiometry results through:[714]

- Evoked otoacoustic emissions (OAE): objective, quick and non-invasive way to assess through to the level of the cochlear and is sensitive to frequency-specific pathology.
- Tone-burst auditory brainstem response (ABR): objective way to detect frequency-specific hearing loss.
- Peripheral audiological assessment such as pure tone audiometry: measures the function of the ear and primary auditory ascending pathways is only limited to the peripheral auditory system, missing central auditory processing deficits and neurological hearing deficits.

Complete audiological assessment should be an objective assessment that can confirm behavioural observations to ensure reliability and avoid missing a significant condition that can be treated. Fitting of hearing aids or cochlear implants are not contraindicated in children and adolescents on the autism spectrum who have hearing impairment. Hearing impairment in autistic children should be treated as for typically developing children.

R 7.16 ***A complete audiological assessment is recommended in all children in whom there is a suspicion for autism so as not to delay the diagnosis of hearing impairment and subsequent management as needed in the event that hearing loss and autism co-exist. [EM 7.12]***

7.5.6 Inborn Errors of Metabolism

There is limited literature on the prevalence of inborn errors of metabolism (IEM) amongst children and adolescents on the autism spectrum. IEM can affect the synthesis or functions of proteins, fats, or carbohydrates, with symptoms and signs presenting because of the accumulation or deficiency of certain metabolites due to affected pathways.[574] Marquez-Caraveo et al. (2021) reported a frequency rate of an IEM, through tandem mass spectrometry, of 3.9% in 51 Mexican unrelated children and adolescents of ages 6–15; 33 of them had a diagnosis of autism.[719] Mitochondrial dysfunction has been the most associated metabolic disorders with autism, with prevalence reported to be 5% in one study.[574] Other disorders include disorders of creatine metabolism, selected amino acid disorders, disorders of folate or vitamin B12 metabolism, and selected lysosomal storage disorders.[574] However, large scale data on this is currently limited.

Please see Chapter 2 on Aetiology and Investigations, Section 2.4.2 for a discussion on the role of investigations for IEM.

GPP 2.14 ***Targeted screening for an inborn error of metabolism may be indicated in selected children on the autism spectrum who present with clinical features such as cyclic vomiting, microcephaly, ataxia, epilepsy, intellectual disability or have a family history of consanguinity. [EM2-8]***

7.5.7 Immune Disorders

7.5.7.1 *Introduction*

Emerging literature suggests a role for neuroinflammation in autism. Studies have indicated that the immune system may be involved in autism. Approximately 25% of children on the autism spectrum have immune deficiency and dysfunction, though most are asymptomatic according to a recent study.[574] Those with GI disorders are more likely to have immunodeficiencies.

Auto-antibodies to brain elements such as myelin basic protein, serotonin receptors, cerebellar tissue and enzymes such as glutamic acid decarboxylase, and antibodies to mitochondria, have been detected in studies of children on the autism spectrum. The presence of auto-antibodies correlated with the severity of autism.[574,720]

Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection, better known as PANDAS and hypogammaglobulinemia have also been associated with autism.[720] Cytokine levels in the blood, brain and cerebrospinal fluid have been noted to be abnormal in individuals on the autism spectrum, with interleukin (IL)-1b, IL-6, IL-8, interferon and Monocyte Chemoattractant Protein – 1(MCP-1) found to be consistently elevated compared to neurotypical controls.[720] However large-scale studies to replicate these findings are currently lacking. Allergies are also noted to be more common in children and adolescents on the autism spectrum, and can influence symptom presentation related to discomfort and pain. Allergic conditions include allergic rhinitis, asthma and atopic diseases. Healthcare professionals should be aware of the potential impact of allergic diseases on behavioural symptoms in autism.[721]

7.5.7.2 *Implications of Immune Disorders in Autism*

Abnormalities in the immune system predisposes the individual to various infective disorders, which in turns increases healthcare costs, hospitalisation and family burden.[574,720] Cytokine abnormalities may be related to GI symptoms in children on the autism spectrum. Low immunoglobulin G (IgG) was reported to be associated with an increased probability of developing autism.[574,720] A study has suggested that children on the autism spectrum who have high titres of seropositive systemic antibodies should be clinically followed up at regular intervals to detect the possible development of symptoms and signs of systemic autoimmune diseases.[574] The presence of allergies increase the level of discomfort and pain and often result in exacerbation of symptoms in the children on the autism spectrum. Behavioural challenges often present as an issue in these children. Alleviation of the allergies can help to improve the clinical status of the child.

7.5.7.3 *Assessment*

A comprehensive history and clinical examination are often sufficient to elicit the symptomatology that allows a healthcare professional to make a diagnosis of an allergy. It is harder to elicit features or risks of autoimmune disorders, so an index of suspicion needs to be present when unusual symptoms present. Laboratory tests can include IgG subclasses, total IgG, and quantitative immunoglobulin in the presence of appropriate symptoms.

In children on the autism spectrum with symptoms of allergy, appropriate treatment can alleviate discomfort and pain, aid sleep and improve functioning. Current evidence is insufficient for routine screening for immunodeficiencies or allergies, and more research is needed in this domain.

7.5.8 **Obesity**

7.5.8.1 Introduction

Obesity is defined as an age-adjusted and gender-specific body mass index at or over the 95th percentile. It is a common, complex, and often persistent chronic disease.[722–724] It is associated with serious health and social consequences if untreated.[725] Prevention and treatment of obesity can be successful.[726,727]

The prevalence of obesity is higher in children and adolescents on the autism spectrum.[728–734] Studies have estimated prevalence rates of obesity to be between 7.9 to 31.8% in children on the autism spectrum.[728–730] The relative risk of obesity in children on the autism spectrum compared with control children was 1.58 in one study,[728] while they had a 41.1% greater risk of development of obesity in another study.[729] Identifying critical periods in the development of obesity is important for early prevention and treatment. Hill et al. (2015) found that children on the autism spectrum tended to be obese earlier from 2–5 years, compared to the general population.[732] The Early Childhood Longitudinal Study Kindergarten Class of 2010-11 (ECLS-K) cohort found a sudden increase in obesity among healthy-weight kindergarten on the autism spectrum between first and second grades, in contrast to controls who had gradual increase.[733]

Children who are overweight are more likely to be overweight in both adolescence and adulthood than children who are of normal weight. Significantly elevated rates of overweight and obesity among children on the autism spectrum compared with control children were found in every age category (2–5 years; 6–11 years; 12–15 years; and 16–20 years).[734] A stabilising period may occur between 6–11 years when obesity was not overrepresented in children on the autism spectrum when compared with those with typical development.[732] Children who had more severe features of autism were more likely to be classified as overweight/obese compared with children with mild features in two separate studies.[735,736]

7.5.8.2 Implication of Obesity in Autism

Obesity puts children and adolescents on the autism spectrum at risk for serious short- and long-term adverse health outcomes later in life,[737–740] including cardiovascular disease, hypertension,

dyslipidaemia, insulin resistance, type 2 diabetes mellitus, non-alcoholic fatty liver disease, orthopaedic problems and impaired motor skills, and sleep-disordered breathing. In addition to physical and metabolic consequences, obesity in childhood and adolescence is associated with poor psychological and emotional health.[741,742] This includes increased stress, depressive symptoms, low self-esteem, poorer cognitive function, attention problems, executive functioning and visuospatial difficulties.

7.5.8.3 Aetiology of Obesity

The reasons for a greater risk of developing obesity in children and adolescents on the autism spectrum are multifactorial. The increased risk of obesity specific to this population is possibly related to medications (antipsychotics, mood stabilizers, serotonin uptake inhibitors), genetic factors (16p11.2 deletion, 15q11.2 duplication), feeding issues (restrictive parent feeding practices, unusual dietary patterns, sensory integration difficulties and food selectivity, mealtime behaviours), physical limitation (low muscle tone and postural instability, coordination and motor control difficulties, difficulties in personal interactions), increased sedentary behaviours and poor sleep patterns.[731,743–745]

7.5.8.4 Sleep Patterns and Obesity in Children and Adolescents on the Autistic Spectrum

There is evidence to suggest an inverse correlation between sleep quantity, and both body mass index and the risk of being overweight or obese.[746–751] Sleep issues are common in children on the autism spectrum. The prevalence of sleep disorders ranged from 2.08% to 72.5% in children on the autism spectrum.[572,752–758] In contrast to neurotypical children whose early childhood sleep problems often resolve, sleep problems in children on the autism spectrum tend to persist and they have a higher rate of sleep problems.[759] Children on the autism spectrum are more likely to be diagnosed with insomnia, circadian rhythm disorder, or sleep-disordered breathing such as obstructive sleep apnoea.[758] Daytime somnolence may reduce activity levels, compounding the risk of unhealthy weight gain.[760]

7.5.8.5 Assessment and Management

Obesity should be managed in children on the autism spectrum similarly to how obesity is managed in children with typical development, with the knowledge that extra attention should be paid to specific medications, genetic conditions, sleep hygiene, feeding issues and physical limitations.[761–763] Primary care physicians should be the main providers to manage overweight and obesity.[764,765] Professionals should encourage prevention measures to reduce these risks, and closely monitor growth over time.

There should be routine discussion of feeding, starting from birth, identifying early feeding disorders, unbalanced dietary preference and providing support and therapy (see Section 7.5.2). Routine screening for social and behavioural challenges and motor difficulties that may affect the amount of physical activity or sedentary behaviour. Medications (if any) should be reviewed regularly to minimise usage and side effects of weight gain and other metabolic issues. Sleep patterns should be monitored as poor sleep quality increases the risk of being overweight and obesity.

GPP 7.17 ***There is an increased risk of obesity in children and adolescents on the autism spectrum, as differences in social interaction, challenges in motor coordination and psychosocial issues in autism can add to increased sedentary risks. Professionals should encourage prevention measures to reduce these risks, and monitor weight, height, body mass index and any significant changes in growth percentiles over time. [EM7-13]***

R 7.18 ***Sleep difficulties are common in children and adolescents on the autism spectrum. Healthcare professionals should monitor sleep patterns and treat sleep dysfunction, as poor sleep quality is associated with various negative consequences, including increased risk of being overweight and obesity. [EM7-13]***

7.5.9 Puberty Challenges in Autism

7.5.9.1 *Introduction*

Puberty is the time in one's life when sexual maturity takes place. The average onset of puberty is 11 years (range 8–13 years) for girls and 12 years (range 9–14 years) for boys. Precocious puberty is a condition when sexual maturity begins earlier than normal, before age 8 for girls and age 9 for boys.[766]

Studies have shown that significantly earlier pubertal developmental occurred in females on the autism spectrum as compared to typically developing girls.[767] There was also evidence that females had advanced pubertal onset compared to males on the autism spectrum. Precocious puberty was also significantly increased amongst those on the autism spectrum in a recent study.[768]

7.5.9.2 *Implications of Early or Advanced Puberty in Autism*

In the general population, early puberty is associated with adverse health outcomes, including breast and endometrial cancer, obesity, type 2 diabetes, cardiovascular disease, short stature and even increased mortality as well as mental health problems.[769] Earlier onset of puberty is also associated with earlier use of alcohol and illegal substance abuse, earlier sexual behaviour and increased risk for delinquency.[769]

Adolescent females on the autism spectrum are at risk for increased emotional reactivity and intensity, with resultant relational, reputational or sexual victimisation and heightened emotional dysregulation, as well as an increased risk for depression.[770,771] This would thus add to the risk for mental health disorders associated with autism. The physical changes in their body related to puberty may also result in greater stress due to difficulties in adaptation to developmental transitions in children on the autism spectrum.

Social withdrawal may intensify during puberty and one-third of individuals on the autism spectrum experience significant psychosocial difficulties.[770]

Maturation disparity was related to depression and externalizing problems in adolescents on the autism spectrum in comparison to the controls. Amongst adolescents on the spectrum, the subgroup of advanced developers showed higher mental health problems (externalising problems, depression and sensory sensitivity).[770]

7.5.9.3 *Assessment of Puberty*

Maturational changes in the sexual system during puberty are seen via both physical and psychological changes. Secondary sexual characteristics signal the onset of puberty involving breast development in females and pubic hair in both sexes. Increase in oestrogen in females result in menstruation (menarche: onset of menses) and breast development. Increase in testosterone in males is associated with phallic growth and voice changes. Social and sexual relationships also develop during puberty. The clinical use of Tanner staging is generally applied to assess for the onset of puberty – Tanner genital stage 2 for boys and Tanner breast stage 2 for girls.

In addition to height and weight, other markers for pubertal onset need to be monitored at follow-up sessions. Early referral for further investigations and specialist management will be critical in those with suspected precocious puberty. Older children and adolescents on the autism spectrum could benefit from sex education and psychological support to aid understanding towards health, pain, hygiene and mood changes. More studies are also needed to study mental health related issues and needs in this group of individuals.

GPP 7.19 ***Healthcare professionals should be aware that there is an earlier onset of puberty, as well as an increased risk of precocious puberty, amongst girls on the autism spectrum as compared to neurotypical children. Routine surveillance, and referral for further evaluation should be done in the presence of symptoms or signs of concern. [EM7-14]***

7.5.10 Visual Challenges in Autism

7.5.10.1 Introduction

There is a high incidence of visual abnormalities in children on the autism spectrum and many of the younger children would not be able to report these differences. Studies have estimated the prevalence of visual impairment amongst this population to range from 0% to 14.9%.[572,772–775] Specific ophthalmologic diagnosis reported include amblyopia, strabismus, optic neuropathy, nystagmus or retinopathy of prematurity. Presenting challenges included blurred vision, double vision, visual suppression, and amblyopia.[776]

Table 7.1 summarises the prevalence of visual problems reported in various studies.

Table 7.1: The prevalence of visual problems in children on the autism spectrum.

Author, Year	N	Prevalence	Refractive errors	Strabismus	Amblyopia
Black et al. (2013)[776]	44	52%	27%	41%	11%
Khabatas et al. (2015)[773]	324	26.9%	22%	8.6%	-
Chang et al. (2019)[774]	2555	71%	42%	32%	19%
Khanna et al. (2020)[775]	51	39%	35%	10%	-

Conversely, looking at those with visual impairment, Do et al. (2017), found that visual impairment was strongly associated with autism, with an overall prevalence rate of autism of 19% amongst those with visual impairment.[715]

7.5.10.2 Implications of Visual Challenges in Autism

Eye pathology could be related to atypical visual behaviours and impaired social communication through visual cues in children on the autism spectrum. Poor visual outcomes will impact on education and daily living as well as psychosocial and emotional disorders. Children on the autism spectrum with ophthalmologic disorders had a significantly lower verbal and performance quotients in one study.[774]

7.5.10.3 Assessment

Based on presenting symptoms, the following can be done as part of the full ophthalmic examination, from as young as 3 years of age: Visual Acuity, Refraction, Photorefraction, Oculomotor Assessment, Binocular Vision Assessment and Eye Health assessment.

GPP 7.20 ***There is an increased incidence of visual problems (e.g., strabismus, refractive errors, anisometropia and amblyopia) amongst children and adolescents on the autism spectrum, which may present as unexplained behavioural issues or academic challenges. Routine vision screening and monitoring for visual problems, should be performed in these individuals and specialty referral be made as needed. [EM7-15]***

7.5.11 Dental Disorders in Autism

7.5.11.1 Introduction

Dental caries, poor oral hygiene and gingivitis were the most common dental conditions observed amongst children on the autism spectrum.[777,778] Other conditions included plaque accumulation, gingival health, malocclusion, developmental anomalies, oral injuries and restorations.[778] Studies have reported that children on the autism spectrum had significantly higher occurrence of caries, severity of caries, bruxism, dental plaque, prevalence of periodontal disease.[779,780] The severity of caries has been associated with age as well use of medications.[781]

It was also noted that the children on the autism spectrum were 2.13 times more likely to receive a referral for general anaesthesia.[779] Overall oral hygiene practices have also been reported to be lower in children on the autism spectrum with respect to regular teeth brushing and presence of healthy gingivae, as compared to typically developing children.[780,781]

7.5.11.2 Implications of Dental Difficulties in Autism

Children on the autism spectrum have difficulty with oral care at home when compared to typically developing children and have been reported to brush their teeth significantly fewer times per week than typically developing children.[779,781–784] More than 50% require assistance with brushing in middle childhood and 27% still required assistance at the ages of 11–18.[783]

Dental treatments have been shown to be associated with greater dental anxiety among children on the autism spectrum, with fears being related to pain, a sensation of pinching or having a tooth pulled.[785] Dental visits were also reported to be more difficult in this group with higher reports of a 'negative experience', and greater difficulty with having the teeth cleaned due to factors like dentist drilling, bright lights, loud sounds, and the need to sit on a dental chair and cooperate with the examination.[783]

There was greater caregiver reported difficulty in locating a dentist willing to provide children on the autism spectrum with care as compared to typically developing children, with a higher proportion reporting being refused dental care by a dentist.[783] Studies of general dentists in the United States show that the majority of the respondents reported that their dental education had not prepared them well to work with special needs populations.[786,787]

7.5.11.3 Assessments and Treatments

The American Academy of Pediatric Dentistry recommends basic behaviour guidance techniques to help any child, with dental care including Tell–Show–Do, voice control, nonverbal communication, and positive reinforcement; these strategies may work for children on the autism spectrum too.[788]

Regular dental evaluations can facilitate earlier detection and preventive treatment in children and adolescents on the autism spectrum. This can avoid them having to undergo treatments in an emergency state when the child may be in higher distress and less likely to be cooperative.

GPP 7.21 ***Professionals should be aware that there is a higher incidence of cavities and gum disease amongst the children and adolescents on the autism spectrum, and these are associated with food selectivity and feeding issues. Routine dental screening and care should be facilitated, especially in the presence of untreated or undertreated cavities and gum disease in these individuals. [EM7-16]***

Abbreviations

ABAS-3, Adaptive Behavior Assessment System; ABR, auditory brainstem response; ADHD, attention deficit hyperactivity disorder; AMPS/ School AMPS, Assessment of Motor Process Skills; ARFID, Avoidant/Restrictive Food Intake Disorder; ASD, autism spectrum disorder; AYCE, About Your Child's Eating; BAMBI, Brief Autism Mealtime Behavior Inventory; BISCUIT, Baby & Infant for Children with aUtIsm Traits; BPFAS, Behavioural Pediatric Feeding Assessment Scale; CBCL, Child Behavior Checklist; CBRS, Conners Comprehensive Behavior Rating Scale; CEBI-R, Children's Eating Behavior Inventory; COPM, Canadian Occupation Performance Model; DCD, Developmental Coordination Disorder; ECLS-K, Early Childhood Longitudinal Study Kindergarten Class of 2010-11; EEG, electroencephalography; GDD, global developmental delay; GERD, gastroesophageal reflux disease; GI, gastrointestinal; MFP, Multidisciplinary Feeding Profile; NICHQ, National Institute for Children's Health Quality; OAE, otoacoustic emissions; PEDI, Pediatric Evaluation of Disability Inventory; PMAS, Parent Mealtime Action Scale; RD, reading disorder; RPs, regulatory problems; SLD, specific learning disorder; SOMA, Schedule of Oral-Motor Assessment; SPD, sensory processing difficulties; TGNC, transgender and gender nonconforming; VABS, Vineland Adaptive Behavior Scales; WeeFIM, Functional Independent Measure; WPATH, World Professional Organization for Transgender Health; YAQ, Youth/Adolescent Questionnaire.

CHAPTER 8: FOLLOW-UP AND PROGNOSIS

An understanding of prognosis of persons on the autism spectrum, both on a short-term basis shortly after diagnosis, as well as on a long-term basis into adulthood, can help caregivers of persons on the autism spectrum to navigate their caregiving journeys better. This knowledge can assist caregivers to be both clear and realistic when considering which interventions and educational pathways they choose for their children/adolescents and moderate their expectations for their growth/developmental trajectories. This can help reduce caregiver stress and lead to more positive relationships between caregivers and the child/adolescent on the autism spectrum.

This chapter outlines: (a) the likely outcomes of children and adolescents on the autism spectrum in adulthood; (b) the longitudinal factors that impact long-term prognosis; and (c) the persistence of challenges associated with autism and new challenges that may occur in adulthood.

8.1 PROGNOSIS IN ADULTHOOD

8.1.1 Key Outcomes in Adulthood

While there was a wide variability in cognitive outcomes across and within various studies regarding prognosis in adulthood, there is a general consensus across studies that outcomes in adulthood in persons on the autism spectrum were, on the whole, poorer than their peers without disabilities. A systematic review of various studies of adults on the autism spectrum by Howlin and Moss (2012) found that despite early recognition and intervention becoming the norm, the percentage of adults on the autism spectrum assessed as having good to very good outcomes, or as living independently or semi-independently, remained low (sometimes below 20%).[789] Another systematic review by Magiati et.al. (2014) found that many studies showed poor cognitive abilities, poor or very poor outcomes in social integration and independence, and the presence of co-occurring medical, behavioural or psychiatric conditions in adulthood. [790] Most studies in Magiati et.al. (2014) also showed low adaptive functioning levels, generally poor functional language, and the continued presence of features of autism, though many studies also showed that there was generally an improvement in these outcomes from childhood.[790]

Howlin's article (2021) indicated that while many studies found that most individuals on the autism spectrum generally improve with age (with respect to severity of symptoms of autism, social skills, language and speech development and degree of ritualistic behaviours and sensory sensitivities), the social outcomes (employment, social relationships and independent living) were still generally poor.[791] For a smaller subset of individuals on the autism spectrum, there can be a persistence or even worsening of features of autism in adulthood.[792]

More recent studies have also indicated the post-school challenges that present to adolescents with autism when they leave school. In the United States context, Howlin (2021) quoted several studies that show considerable challenges for both children on the autism spectrum with moderate to severe cognitive challenges, as well as individuals described as "high-functioning" (typically with normal cognition).[791]

For those with moderate to severe cognitive challenges, independence as adults is highly unlikely, meaning that they would continue to need substantial support in adulthood. This highlights the importance of planning early for post-school transitions. Adolescents on the autism spectrum with more severe cognitive challenges, need to secure post-school placements to reduce the likelihood of regression in young adulthood.[791]

Even amongst those with lower support needs, many continue to experience social, emotional and/or behavioural challenges, with limited independence and requiring continued support, and they may also continue to have limited social participation outside of the family.[791] Specifically, while employment chances can be improved for this group through the provision of support from educational institutions

and families[793] (see below for more details), many studies indicate that many of these persons on the autism spectrum continue to suffer from higher levels of unemployment and under-employment as compared to their peers.

Many children on the autism spectrum also tend to develop mental health challenges in adolescence and adulthood (see Chapter 7, Section 7.3). While prevalence rates reported can range from 20 to 25% to over 75%,[791] the types of conditions found to be common were more consistent across studies. Symptoms of anxiety and depression (with related difficulties of phobias, obsessive-compulsive disorders [OCD] and post-traumatic stress disorders [PTSD]) and attention-deficit hyperactive disorders (ADHD) were found to be common in many studies (e.g., Howlin and Moss [2012][789]). The risk of suicide, suicidal ideations and suicide attempts were found to be higher than normal, among adolescents on the autism spectrum (especially, teenage girls) who were cognitively and verbally able.[791,792]

8.2 PROGNOSTIC FACTORS

8.2.1 Long-term Longitudinal Factors

Several systematic reviews have found strong evidence that adult outcomes in several domains – cognitive functioning, social functioning and integration, and speech/language/communication development – are correlated with certain longitudinal predictors, e.g., IQ and severity of autism symptoms in childhood.

The well-established determining prognostic factors for outcomes in adulthood include the presence of co-occurring intellectual disability (ID), early language development, and the severity of symptoms of autism in early life.[792] Generally, autistic individuals with co-occurring ID, those without significant early development in language acquisition, and those with the most severe symptoms of autism when young, tend to have poorer outcomes in adulthood.[789]

8.2.2 Contextual Prognostic Factors

Notwithstanding the presence of the long-term longitudinal factors above, it was found that several other contextual factors can also have a significant impact on outcomes in adulthood, namely the extent to which mothers were nurturing and positive in their parenting, and the level of inclusion experienced by the child or adolescent on the autism spectrum in their formal education.

Autistic children whose mothers made more positive remarks about them were significantly more likely to have a more desirable trajectory of improvement through adolescence into adulthood. In contrast, autistic children who were subject to greater levels of maternal criticism (e.g., signs of the mother's antagonism, negativity, disgust, harshness and lower responsiveness) predicted greater levels of externalising behaviours of concern (overactivity, poor impulse control, noncompliance and aggression) in these children,[794] which in turn could trigger higher levels of maternal anxiety and distress.

GPP 8.1 ***Interventions that promote positive parenting, mothering and fathering, should be encouraged. This should include support structures which help parents to understand their children/adolescent's autism and the associated challenges as early as possible. Parent training on how to respond to behaviours of concern and their participation in support groups should be encouraged. [EM8-1]***

Children on the autism spectrum who were exposed to full or partial inclusion also experienced a more desirable growth trajectory than those in a segregated setting, even after accounting for levels of functioning as defined by the number of symptoms of autism and the presence of ID.[794] This reflects that children in more inclusive settings experience more opportunities to practice their adaptive functioning skills than those in less inclusive settings. It is also critical that children and adolescents on the autism spectrum are afforded opportunities to explicitly learn adaptive functioning skills.

GPP 8.2 ***The focus of intervention for children and adolescents on the autism spectrum should address the holistic needs of these individuals across the entire lifespan. This includes addressing adaptive functioning and emotional wellbeing, in addition to academic achievement, in order to maximise the quality of life of the individual on the autism spectrum in the long run. The goals of the child/adolescent and his/her family should also be taken into consideration. [EM8-1]***

8.3 PERSISTENCE OF CHALLENGES ASSOCIATED WITH AUTISM AND NEW CHALLENGES IN YOUNG ADULTHOOD

Another area of concern that caregivers often have is the persistence of challenges associated with caregiving for children and adolescents on the autism spectrum. As mentioned above, most individuals on the autism spectrum generally improve with age. Nonetheless, some challenges persist for persons with autism into adulthood, and new challenges can also emerge in late adolescence or young adulthood.

Several studies have indicated that persons on the autism spectrum suffer from a higher rate of psychiatric conditions than the general population,[789,794] especially in adulthood. The percentage of young adults with autism who had no daytime activities who had a co-occurring psychiatric condition was found to be as high as 86%.[795] This indicates the critical importance of ensuring that graduates of both our Special Education (SPED) and mainstream schools are successfully transitioned into suitable post-school settings where they can be further supported.

Factors that could trigger new-onset psychiatric conditions were negative life events or changes such as a change of residence, caregivers or familiar routines.[796] Such events could be triggered by sudden events such as the bereavement of caregivers, or by more predictable transitions such as graduation from school.

8.4 TRANSITIONS INTO ADULT SETTINGS IN SINGAPORE

As children on the autism spectrum transition into adolescence and get closer to their point of graduation from school, caregivers become increasingly concerned about their post-school transitions. Caregivers often wonder about their children/adolescents' chances to transition successfully into the following settings:

a) further education in institutes of higher learning
b) paid, open employment
c) supported employment
d) sheltered workshops
e) day activity centres
f) not in further education, employment (of any kind) or in sheltered workshops or day activity centres, i.e., being fully cared for at home, or accessing community resources for part-time care.

(It is important to note that a very small number of autistic children transition into 24/7 residential care settings or long-stay wards in the Institute of Mental Health after graduation from school, as their parents can no longer care for them.)

SPED schools begin the process of planning for the post-school transition of their students on the autism spectrum early, i.e., when the students are 13 years of age. For children on the autism spectrum who are in SPED schools, caregivers should be encouraged to discuss the transition plans for their children early. To do so, caregivers can reach out to the Transition Planning Coordinators in these SPED schools.

For children on the autism spectrum who are in mainstream schools, caregivers may also want to give due consideration not only to their children's academic progress as they progress through the

educational system, but also their social adaptation in school and their development of executive functioning skills which will be critical to their transition to Institutes of Higher Learning, as well as employment and independent living.

For those who are likely transitioning to open employment after school (rather than higher education, day activity centres or sheltered workshops), caregivers can seek the help of agencies such as Employment and Employability Centre (https://www.autism.org.sg/core-services/e2c), Trampolene (https://trampolene.org/) and Inclus (https://inclus.sg/) for additional support in job placements.

For those transitioning to day activity centres, sheltered workshops or residential facilities, the Enabling Guide published by SG Enable provides more information on these services run by various SSAs. (https://www.enablingguide.sg/im-looking-for-disability-support/child-adult-care/).

GPP 8.3 ***Systematic transition planning should be encouraged for predictable major transitions for children and adolescents on the autism spectrum. Such transition planning should be proactive, holistic and person-centric. Of particular importance is the need for early transition planning for adolescents on the autism spectrum ahead of their graduation from mainstream or SPED school. [EM 8-1]***

(See also GPP 5.18 on transition from one educational setting to another)

Abbreviations

ADHD, attention-deficit hyperactive disorders; ID, intellectual disability; OCD, obsessive-compulsive disorders; PTSD, post-traumatic stress disorders; SPED, special education.

CHAPTER 9: CAREGIVER AND FAMILY SUPPORT

Support for caregivers and families of children/adolescents on the autism spectrum has been recognized internationally and nationally as a key strategic thrust to improving short- and long-term outcomes of persons with disabilities and their family.[2,375,797] This chapter turns the focus onto the caregivers and the families of children/adolescents on the autism spectrum. The term "caregiver" is used in this guideline to be inclusive of parent, sibling, family member, spouse or relative who has taken on the responsibility of looking after a child/adolescent with autism. This chapter covers review and synthesis of the current knowledge and evidence on supporting caregivers and family of children/adolescents on the autism spectrum to put forth evidence-based recommendations for professionals to support caregivers and families optimally in Singapore.

9.1 WHY IS IT IMPORTANT TO SUPPORT CAREGIVERS AND FAMILIES OF CHILDREN AND ADOLESCENTS ON THE AUTISM SPECTRUM?

9.1.1 Impact of Autism on Caregiver and Family

The persistent nature and difficulties associated with autism such as marked differences in social interaction and communication, restricted patterns of behaviours, and emotional and behavioural challenges, not only affect the autistic individuals, but also their families' lives. Parents of children/adolescents on the autism spectrum were reported to experience high levels of stress, which include caregiving stress, physical exhaustion, social isolation, marital and financial strain.[798–802] Some of the factors which influence parental stress level are the availability of social and financial support, severity of autism symptoms, parents' understanding of autism and parents' worries for their child's future.[803]

The government provides financial support for individuals with disabilities. Subsidies based on means-testing are available at early intervention centres, childcare centres and day activities centres. Other financial assistance includes caregivers training grant, Migrant Domestic Worker Levy Concession, Handicapped Child Relief and Assistive Technology Fund. For more information on financial assistance, please refer to the Enabling Guide[t] and Inland Revenue Authority of Singapore website[u].

GPP 9.1 ***Professionals should be equipped with the understanding of how autism can affect caregivers and families in terms of social, economic, physical and mental health to support caregivers and families optimally. [EM 9-1]***

9.2 HOW DO WE SUPPORT CAREGIVERS AND FAMILIES OF CHILDREN/ADOLESCENTS ON THE AUTISM SPECTRUM?

9.2.1 Important Considerations When Supporting Caregivers and Families

9.2.1.1 Providing Information and Support for Caregivers

Parents and caregivers require ongoing information to help them understand the autism diagnosis, education and intervention options, and sources of social and financial support. Parent training and support programmes are offered by certain special education (SPED) schools, hospitals and social service agencies.

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[t]Enabling Guide: https://www.enablingguide.sg/.
[u]Inland Revenue Authority of Singapore – financial assistance: https://www.iras.gov.sg/taxes/individual-income-tax/basics-of-individual-income-tax/tax-reliefs-rebates-and-deductions/tax-reliefs/qualifying-child-relief-(qcr)-handicapped-child-relief-(hcr).

9.2.1.2 *Explanation on the Autism Diagnosis*

Appropriate written and verbal information on the diagnostic screening and assessment should be provided. Caregivers, family members, siblings and/or young people on the autism spectrum will require information on autism and the post-diagnosis intervention or services available. The information provided should be appropriate to the child/adolescent's age and ability level. Affirmation of the autistic identity is also important. Caregivers and their families are encouraged to attend regular training on psychoeducation and intervention strategies. For further information, please refer to the Autism Network Singapore[v], Autism Resource Centre[w] and Enabling Guide[x] website.

9.2.1.3 *Intervention and Education*

Caregivers will require information and support on early intervention and education options to facilitate their decision on the appropriate early intervention and/or education placement for their child with autism, taking into consideration their child's cognitive ability and autism severity. For information on early intervention and education options, please refer to the SG Enable[y], Early Childhood Development Agency[z] and Ministry of Education website and guides[aa], as well as to Chapter 5 in this CPG on Education and Transition.

For children/adolescents who present with significant challenging behaviours, professionals would need to make appropriate referrals for further medical evaluation and/ or behavioural support such as occupational therapy and psychotherapy.

9.2.1.4 *Social, Emotional and Financial Support*

Information on where parents could seek emotional and caregivers support, and the available financial schemes should be provided. In addition to providing the post-diagnosis information, professionals would need to be sensitive to the caregivers' and their families' emotional reaction in response to their child's autism diagnosis. Grief and loss might be experienced by caregivers as they journey with their child/adolescent with autism at different developmental and life stages.[798,800,803] Furthermore, the behaviours of the child/adolescent on the autism spectrum may have some possible impact on his or her family's life. Therefore, the emotional needs of siblings and extended family would need to be taken into consideration. Where necessary, professionals would need to make appropriate referral for supportive counselling or respite care. For more information on caring for caregivers, please refer to the Caregiver Learning Roadmap on the Enabling Guide website[bb].

Parent support Parent support includes both informal social support, and formal support by professionals. Informal social support would include support from spouse, family members, community, other families of children/adolescents on the autism (autism community), support group, and online support. Similarly, there is some emerging evidence of potential benefits of facilitating access to peer support services for older adolescents with average verbal and cognitive abilities. The quality of the

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[v]Autism Network Singapore: https://sgautism.org/.
[w]Autism Resource Centre: https://www.autism.org.sg/.
[x]Enabling Guide: https://www.enablingguide.sg/.
[y]SG Enable: https://www.sgenable.sg/; https://www.enablingguide.sg/im-looking-for-disability-support/therapy-intervention/early-intervention-programme-for-infants-children
[z]Early Childhood Development Agency: https://www.ecda.gov.sg/
[aa]Ministry of Education websites: https://www.moe.gov.sg/special-educational-needs; https://www.moe.gov.sg/-/media/files/special-education/parents-guide-children-special-educational-needs.ashx
[bb]For more information on caring for caregivers: https://www.enablingguide.sg/caring-for-caregivers/new-to-caregiving

existing relationship between the parents and their family members and/or community can influence the perceived social support experienced by the parents.[803] In general, a close relationship with family members and understanding from the community would result in greater social support for parents. Parent support from professionals would include psychoeducation of autism, and care and coordination of services.[804] To strengthen caregivers' capacity and resilience in parenting their child on the autism spectrum, parents would benefit from having access to both informal social support and formal support by professionals.

Sibling support Siblings of children on the autism spectrum may face greater challenges than other typically developing children. Some of the challenges might include, impact on one's self and personal identity, impact on sibling relationships, and behavioural and emotional problems.[805,806] However, not all siblings have poor outcome and/or poor sibling relationships.[805,807] To enhance siblings' functioning, parents and professionals should try to ensure siblings have access to age-appropriate information on autism and how it relates to their siblings with autism, social support, and counselling and support when necessary.

GPP 9.2 ***Professionals should provide caregivers and family with information tailored to the child's/ adolescent's developmental age and needs and also support caregivers and families in accessing appropriate services for the child/ adolescent as well as caregivers. [EM9-2, 9-3, 9-4]***

GPP 9.3 ***Professionals should strive to adopt a collaborative and family-centred approach in supporting caregivers towards optimal outcomes for a child/ adolescent on the autism spectrum, the caregiver and the family. [EM9-2, 9-3, 9-4]***

GPP 9.4 ***Professionals should assess emotional well-being of the caregiver and how the family is coping to provide necessary resources or support in the holistic care of a child and adolescent on the autism spectrum. [EM9-2, 9-3, 9-4]***

9.2.2 Lifespan Perspective in Supporting Caregivers and Families

Autism is a neurodevelopmental condition with long-term implications for the individual and his/her family. A lifespan perspective recognises that as an individual grows and develops with time, he or she will need to face new opportunities and challenges at different life phases.[6,9] Mutual respect and collaboration among professionals and families help to empower caregivers and support them in their caregiving journey.[808,809] Therefore, caregivers and families will require information and support across the individual's lifespan and transition points.

9.2.2.1 Physiological Changes and Puberty

Caregivers' play an important role in supporting their children on the autism spectrum before and during the adolescent phase. Due to their differences in social and communication skills, children and adolescents on the autism spectrum require education and coaching on managing their social, emotional and physiological development.[810] Sexual education and guidance should be initiated at an early age and tailored to the individual's ability. Therefore, caregivers will require information on how to teach their children on managing physical arousal, masturbation, menstruation and/or romantic feelings.

9.2.2.2 Transitions - Information on The Supports Available in School and Community

Due to autism's characteristic features, such as preference for routines and difficulties with changes, some children/adolescents on the autism spectrum may have more difficulties than others in adapting to changes and transitions. Some of the changes include change in physical environment, teachers, time-tables and school hours. Therefore, caregivers would benefit from having information sharing or guidance by professionals on how they could support their children/adolescents at each transition point.[6] For example, from preschool to formal schooling in a SPED or mainstream school; or from formal schooling to further education, employment or adult care services.

9.2.2.3 *Planning for the Future*

Several studies have indicated parents' anxiety and worries about their child/adolescent's future.[803,811,812] Caregivers would require information on post-schooling options, such as day activity centres, sheltered employment or supported employment, and where necessary, information on setting up a trust and application for deputyship. For more information, please refer to the Caregiver Learning Roadmap in the Enabling Guide, and the Autism Enabling Masterplan.[cc]

GPP 9.5 ***Professionals should support caregivers and family during the child's/ adolescent's transition across the lifespan, especially in terms of future care planning. [EM9-4]***

9.3 WHAT TYPE OF CAREGIVER EDUCATION AND TRAINING IMPROVES CHILD/ADOLESCENT, CAREGIVER AND FAMILY OUTCOMES?

The usefulness of caregiver education and training in improving child and youth outcomes has been extensively researched in home and day-care setting since the 1970s.[813–822] Improvement in behaviour, parent-child interaction, communication, sleep and core symptoms of autism were evaluated. Many terminologies have been used inconsistently to denote parent or caregiver support, education, and training.

This review adopted the term "Caregiver Support, Education and Training" (CET) as synonymous with commonly used terminologies such as Parent Education and Training (PET),[823] Parent-mediated Early intervention,[824,825] Parent or Caregiver Education[826] or Psycho-education programmes, Parent Training,[827,828] Parent-Mediated Interventions (PMI),[829,830] Parent interventions,[831] Parent-focused intervention[832], Parent-implemented interventions (PII),[23] Caregivers Skills Training (CST).[833] Herein, CET is defined as "the passing of information or skills to parents/caregivers using a range of modalities (didactic, role-play, discussions, video guidance) in a context where parents/caregivers and trained facilitators are the direct participants". The primary emphasis is on knowledge and skill transfer to parents/caregivers and the priority participants are parents/caregivers and not the parent-child dyad (e.g., the child is not present in the session/consultation room while the intervention is being delivered).

Existing CETs vary in format, setting, intensity, duration, and target age.[824,828,834] These CETs might be delivered in groups, one-to-one or self-directed learning. The training settings could be in clinic, school, home-based services or through telehealth. The interventions might vary from low to high intensity (e.g., from bi-monthly to weekly meeting with a therapist); and from a few days to a few years in duration. Some interventions might target a specific age group (e.g., preschoolers, school-going children or adolescents).

Current CETs are centred around three themes: autism core skills, maladaptive behaviours and parental outcome.[828,834] Interventions that focus on autism core skills include training in communication and language skills, interaction and play skills, and daily living skills. Interventions that focus on maladaptive behaviours include training in functional behavioural analysis, appropriate use of reinforcement, teaching alternative communicative response, and modulating child affect and arousal. Finally, interventions that focus on parental outcome aim to facilitate parents' attunement and responsiveness, create opportunity to discuss about child's behaviours and parents' coping strategies, and in so doing, parents receive information and support from professionals.

Major practice guidelines (such as Individuals with Disabilities Education Act [2004];[835] National Autism Center [2015];[24] World Health Organization, 2013[797]) and a substantial body of research have since highlighted the effectiveness of CET in improving child/adolescent and caregiver outcomes. In a recent review conducted by the National Professional Development Center on Autism Spectrum Disorders[836]

[cc]For more information on transitions: https://www.enablingguide.sg; https://enablingmasterplan.autism.org.sg/

and its updated review conducted by the National Clearinghouse on Autism Evidence and Practice,[23] CET has been identified as one of the autism practices with best evidence. A number of reviews[210,823,837,838] and meta-analyses[824,827,829,831] have synthesized and interpreted the overall effects of CET. Recent review by Liu et al. (2020) analysed studies in Mainland China, Hong Kong and Taiwan yielded results consistent with earlier studies.[830]

9.3.1 Possible Benefits of CET on Child/Adolescent Outcomes

Review of six most recent meta-analysis[824,827,829–831,839] revealed that CET improves outcomes of child/ adolescent on the autism spectrum in terms of autism symptom severity, language, communication and anxiety.

As caregivers spend a significant amount of time with the child on the autism spectrum, including caregivers as intervention mediators would help to facilitate the child's acquisition and generalisation of new skills, and empower parents.[840] Training parents as mediators of early intervention allows intervention to begin as early as possible. It is often aimed at providing parents with interaction strategies to enhance the child's earliest social relationships. It is important, given the nature of the child's developmental differences, that parents support the child in establishing shared interest in each other and in objects, and learn the power of imitation. If parents act in a way that is 'synchronous' with their child's focus and intentions, then language and communication are enhanced.[841] The secondary benefits may be reduced frustration for the child, thus reducing disruptive behaviours and emotional sequelae, e.g. anxiety.

Where CET is an adjunct to an education-based intervention, the amount of autism-appropriate intervention can increase, with generalisation of child learning across different people and environments. Many promising focused intervention practices and comprehensive treatment models (CTMs) involve components of naturalistic interventions for teaching pivotal skills in natural environments and parent-implemented approaches where caregivers learn strategies to better support their children's development.

9.3.2 Possible Benefits of CET on Caregiver Outcomes

In terms of effect on caregiver outcomes, two meta-analyses were reviewed.[824,831] CET was found to improve caregiver outcomes in terms of parent-child interaction or parental synchrony.

By and large, CET helps to increase caregivers' confidence and skills. Equipping caregivers with the necessary information and skills allows them to provide home-based support for their children/adolescents on the autism spectrum, so as to complement the work of early intervention services or allied health professionals. Furthermore, training caregivers in new skills has frequently been carried out in groups, allowing for mutual support and potential reduction of caregiver stress.

Indeed, empowering parents with the knowledge and skills to effectively cope with autism-related difficulties can result in a wide range of benefits to the families, inclusive of but not limited to reduced disruptive behaviours,[827] improved parent–child interactions,[829] and decreased parental distress.[831]

R 9.6 ***Caregiver education and training programmes should be incorporated in intervention programmes for child and adolescents on the autism spectrum whenever possible as there is evidence to suggest positive effects on outcomes for both the child/adolescent as well as caregiver. [EM9-5]***

9.4 WHAT CAREGIVER SUPPORT SERVICES ARE AVAILABLE IN SINGAPORE FOR CAREGIVERS AND FAMILIES OF CHILDREN/ADOLESCENTS ON THE AUTISM SPECTRUM?

9.4.1 Overview of The Current Landscape of Caregiver Support Services in Singapore

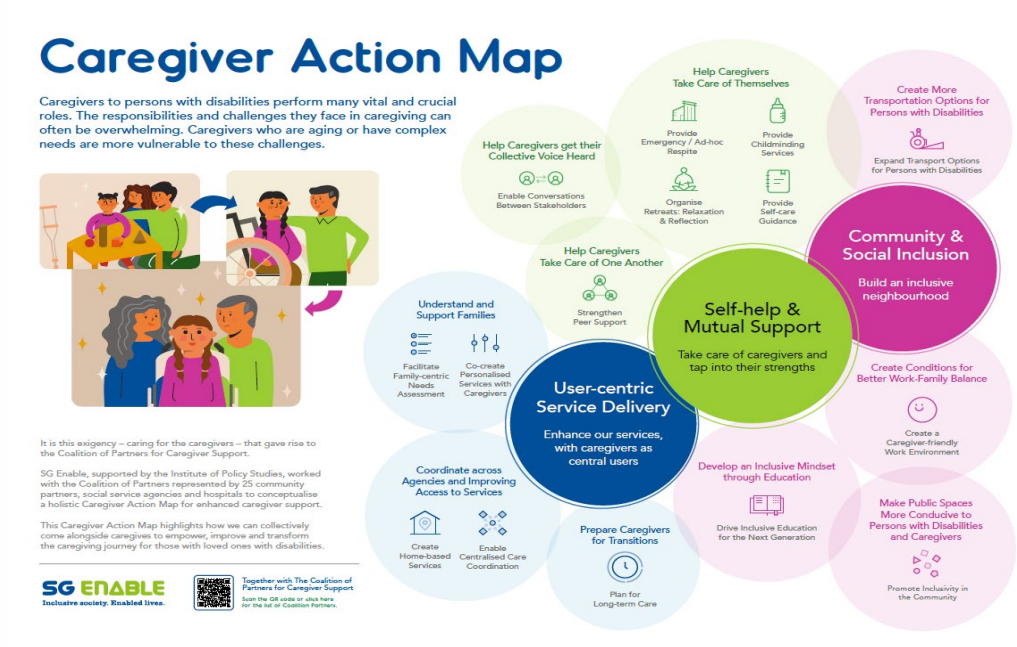
The caregiver support landscape in Singapore has evolved much since the first enabling masterplan (2007-2011).[842] The importance of strengthening support for caregivers was also highlighted during Emerging Stronger Conversations & Conversations on Singapore Women's Development.[843,844] The development of the Caregiver Action Map (see infographic below) by SG Enable in collaboration with social service agencies, community partners, hospitals and the Institute of Policy Studies in 2019 further expounded on the need to develop services that are user-centric ecosystem to promote self-help and peer support, and last but not least, build inclusive neighbourhoods in the community.

Building on these cumulative efforts, an Alliance for Action for Caregiver[dd] of persons with disabilities were convened in July 2021 to implement programmes that improve self-help and peer support, as well as build inclusive communities. Two key projects are included in Project 3i and Community Circle. The Project 3i by special needs caregiver support charity CaringSG[ee] aims to connect caregivers with others in the community, provide befriending and peer mentorship by trained caregivers, and provide caregivers and families with complex needs with advisory support from professional volunteers and a community support team.

The latest Enabling Masterplan 2030[845] delineated 29 recommendations along 3 strategic themes spanning 14 focal areas, which cover the life stages and various needs of persons with disabilities and their caregivers. Specifically, for Area 7 on Caregiving Support, the target by 2030 is for caregivers of persons with disabilities to have access to caregiving support, including respite services and future care planning. Access would cover a variety of factors such as awareness, ease of application, affordability, perceived quality, capacity, and suitability of services. Specifically, for caregiving support, two recommendations were put forth. Recommendation 12 purports enhancing respite options and support for caregivers, to help them care for loved ones with disabilities in the community. Recommendation 13 is on supporting caregivers in planning for the future and prioritising the needs and choices of their family member with disabilities.

[dd]For more information, please refer to: https://www.straitstimes.com/singapore/politics/support-for-caregivers-of-those-with-special-needs-available-beyond-schools

[ee]For more information on CaringSG, please refer to: https://caring.sg/.



Source: https://www.sgenable.sg/docs/default-source/default-document-library/resources-library/caregiver-action-map.pdf?sfvrsn=99ad13c4_3

9.4.2 *Resource Listing of Caregiver Support Services in Singapore*

Many useful directories/resource listings are available to support caregivers in accessing appropriate services for their dependents and themselves. This includes the SG Enable's Enabling guide[ff] and CaringSG's[gg] member resources.

CETs for children and adolescents with autism are currently mainly provided by specific social service agencies where the child is receiving services. These include Autism Association Singapore, Rainbow Centre, AWWA, St Andrew Autism Centre, Autism Resource Centre and other early intervention centres and special schools. On the other hand, there are institutions and agencies which are increasingly providing CETs that are not bounded by where the child is receiving services e.g., ARC Learning Academy[hh], Rainbow Centre -Training and Consultancy[ii], SGEnable's Step One training, CaringSG's CAREconnect programmes and CAREbuddy service[jj] and Caregiver Alliance Limited[kk]. In terms of dedicated medical and dental care for persons with disabilities, these are available at Mount Alvernia Outreach Medical Clinic (MAOMC) and MINDS Developmental Disabilities Medical Clinic[ll].

Case coordination services to support caregivers in accessing appropriate services, as well as home-based CET are now provided by several agencies, including:

1. SG Enable's Service Coordination and Advisory team
2. CaringSG's CAREwell community support team[mm]

[ff]For more information on the Enabling guide, please refer to: https://www.enablingguide.sg/.
[gg]For more information on CaringSG, please refer to: https://caring.sg/.
[hh]ARC Learning Academy: https://learningacademy.autism.org.sg/
[ii]Rainbow Centre – training & consultancy: https://rainbowcentre.org.sg/training/
[jj]CaringSG's programme and service: CAREconnect programme (https://caring.sg/careconnect/) and CAREbuddy service (https://caring.sg/carebuddy/)
[kk]Caregivers Alliance programmes & support: https://www.cal.org.sg/programme-support
[ll]MINDS Developmental Disabilities Medical Clinic: https://www.minds.org.sg/other-services/medical-services/
[mm]CaringSG's CAREwell: https://caring.sg/carewell/

3. SG Assist
4. ABLE (Caregiver Support and Case Management)
5. Rainbow Centre (Family Empowerment Programme)[nn]
6. SPD's Specialised Case Management Programme[oo]
7. MINDS Disability Case Management Programme, and MINDS Home-Based Care Services[pp]

In time to come, caregiver support programmes for children and adolescents on the autism spectrum in Singapore are expected to be provided by more agencies and also increase in variety. Further research would aid in standardising CET for autism, as well as to evaluate cost-benefits and social return of investment of CET programmes.

Abbreviations

CET; Caregiver Support, Education and Training; CST, Caregivers Skills Training; CTMs, comprehensive treatment models; PET, Parent Education and Training; PII, Parent-implemented interventions; PMI, Parent-Mediated Interventions; SPED, special education.

[nn]Caregivers – Rainbow Center, Singapore. https://rainbowcentre.org.sg/caregivers/
[oo]SPD's Specialised Case Management Programme: https://www.spd.org.sg/specialised-case-management-programme/
[pp] MINDS Disability Case Management Programme (https://www.minds.org.sg/disability-case-management-programme/) and MINDS Home-based Care Services (https://www.minds.org.sg/for-adults/home-based-care-services/)

CHAPTER 10: PROFESSIONAL TRAINING

Care for the child or adolescent on the autism spectrum is delivered by an entire eco-system of professionals who serve the child, adolescent and the family directly as well as indirectly. This community encompasses various professionals and entities including but not limited to those in primary care (healthcare professionals such as nurses, general practitioners, general paediatricians), specialist medical providers (developmental and behavioural paediatricians, psychiatrists, dentists, other specialist medical professionals), allied health professionals (speech and language therapists, occupational therapists, psychologists, physiotherapists, podiatrists, social workers), early intervention centre professionals, educators across various levels of education, and personnel who may work indirectly with individuals on the autism spectrum such as security personnel and support staff in schools. It is important that this whole community works towards the goal of providing optimal care for these children and adolescents. Professionals who are on the autism spectrum can also bring their own lived experiences to their workplaces. Lack of information and training about autism has been identified by professionals in multiple sectors as a barrier in their field.[846–848]

As part of efforts to improve care provided to individuals on the autism spectrum, it is recommended that any professional who works with children and adolescents on the autism spectrum indirectly or directly, be provided with access to information on autism. Learning can be skills-based or knowledge-based and can include varied forms of delivery, depth and context; this should be tailored to the needs and work setting of the specific personnel. Learning should also include information on neurodiversity, recognise autism as a form of identity, and involve individuals on the autism spectrum where possible to facilitate exchanging of information. Information on resources to provide further materials and facilitate self-directed learning as needed should also be facilitated. Resources provided should also promote neurodiversity-affirming language.

GPP 10.1 ***Access to autism related information should be provided for staff who interact with/care for children and adolescents on the autism spectrum (directly/indirectly). Extent and depth of information should be tailored to the specific professional's needs. [EM10-1]***

10.1 PRIMARY AND TERTIARY CARE HEALTHCARE PROVIDERS

Formal training of hospital-based healthcare providers has been shown to improve observer-rated staff knowledge, self-rated competency and attitudes towards autism.[849,850] Training programmes that have been studied varied depending on the country and context of use, but have been in the form of didactic teaching lectures, inter-disciplinary case-based discussions, experiential training and video-based training. Peer learning approaches through peer observation and peer supervision would be a cost-effective approach towards training for primary care providers. Formal training courses and/or further post-graduate qualifications may supplement these peer learning strategies.

There is no consistent singular training programme that has been evaluated across multiple settings thus far. Content of training may include recognition of symptoms and diagnosis of autism, care coordination and facilitation of appropriate services for children and adolescents on the autism spectrum.[851] Whether such training can directly improve patient care beyond other factors is also unclear and an area for further research.

10.2 ALLIED HEALTH PROFESSIONALS

All allied health professionals working with children and adolescents on the autism spectrum should have the appropriate qualifications recognised by their respective professional bodies.

In Singapore, personnel providing occupational therapy, physiotherapy, and speech-language therapy to individuals on the autism spectrum must be registered with the Allied Health Professions Council (AHPC) and possess a valid practicing certificate (https://www.healthprofessionals.gov.sg/ahpc) as

mandated by the Allied Health Professions Act 2011 (https://sso.agc.gov.sg/Act/AHPA2011). Psychologists should be registered with the Singapore Register of Psychologists or other relevant professional bodies recognised by the Singapore Psychological Society.

10.3 AUXILIARY SUPPORT SERVICES/STAFF WITHIN THE BROADER MEDICAL AND EDUCATION CONTEXT

There has been growing awareness about the need for formal autism-related training, for different professionals who work and interact with individuals on the autism spectrum (directly or indirectly). There has been a number of studies demonstrating potential benefits of formal training programmes in improving staff knowledge, attitudes, and self-perceived competency in care for children and adolescents on the autism spectrum. These include studies on law enforcement officers which demonstrated improved interaction with individuals on the autism spectrum, knowledge and self-confidence.[852,853] Another study on a training programme for security officers in a children's hospital showed improved self-reported comfort in interacting with children on the autism spectrum and knowledge of autism after the training.[854] There have been similar studies showing improved knowledge and confidence in interacting with individuals on the autism spectrum among hospital support staff, teachers and the broader autism community of parents and community members.[855–857] However, there is no singular training programme or format that has been consistently studied. Further, evidence on whether these programmes directly improve care of children/adolescents on the autism spectrum is not currently available.

APPENDIX 1: GUIDELINE DEVELOPMENT GROUP AND EXTERNAL REVIEWERS

MAIN WORKGROUP MEMBERS

No.	Name	Subgroup Lead	Subgroup Contribution
1	**Dr WONG Chui Mae** ***(CPG Co-Lead)*** *Senior Consultant Paediatrician* Departments of Child Development and Neonatology, KK Women's and Children's Hospital	Screening and Diagnosis	1. Screening and Diagnosis 2. Pharmacological Treatment 3. Complementary and Alternative Treatment
2	**Dr Aishworiya RAMKUMAR** ***(CPG Co-Lead)*** *Consultant Paediatrician* Child Development Unit (Division of Developmental and Behavioural Paediatrics), Department of Paediatrics, KTP-NUCMI, National University Hospital	Professional Training	1. Aetiology and Investigations 2. Complementary and Alternative Treatment 3. Professional Training
3	**Adj Assoc Prof Sharifah Mariam ALJUNIED** *Principal Educational Psychologist* Special Educational Needs Division, Ministry of Education	Education and Transition	1. Education and Transition 2. Professional Training
4	**A/Prof Daisy CHAN Kwai Lin** *Senior Consultant* Department of Neonatal and Developmental Medicine, Singapore General Hospital *Visiting Senior Consultant* Department of Child Development KK Women's and Children's Hospital	Aetiology and Investigations	1. Aetiology and Investigations
5	**Ms Janice CHEONG Mun Yi** *Psychologist* Department of Psychological Medicine, KK Women's and Children's Hospital		1. Screening and Diagnosis 2. Co-occurring Conditions
6	**Mr Bernard CHEW** *Chief Executive Officer* St Andrew's Autism Centre	Follow-up and Prognosis	1. Follow-up and Prognosis 2. Caregiver and Family Support
7	**Dr CHIN Chee Hon** *Senior Consultant Psychiatrist* Department of Developmental Psychiatry, Institute of Mental Health		1. Pharmacological Treatment 2. Follow-up and Prognosis
8	**Dr Sylvia CHOO Henn Tean** *Senior Consultant Paediatrician* Department of Child Development, KK Women's and Children's Hospital	Complementary and Alternative Treatment	1. Complementary and Alternative Treatment 2. Follow-up and Prognosis 3. Caregiver and Family Support
9	**Dr Angelia CHUA Hwee Ling** *Family Physician, Consultant* National Healthcare Group Polyclinics		1. Professional Training

10	**Ms Magdalene FOO Tze Suang** *Principal Medical Social Worker* Department of Developmental Psychiatry, Institute of Mental Health	Caregiver and Family Support	1. Caregiver and Family Support
11	**Dr GOH Tze Jui** *Principal Clinical Psychologist* Department of Developmental Psychiatry, Institute of Mental Health	Intervention	1. Screening and Diagnosis 2. Intervention 3. Co-occurring Conditions
12	**Dr Majeed KHADER** *Principal Consultant Psychologist* *Chief Psychologist* Ministry of Home Affairs Singapore		1. Caregiver and Family Support
13	**Mrs Stephenie KHOO Koon Miang** *Deputy Executive Director* Autism Resource Centre (Singapore)		1. Intervention 2. Professional Training
14	**Dr KOH Hwan Cui** *Principal Psychologist* Department of Child Development, KK Women's and Children's Hospital		1. Screening and Diagnosis 2. Intervention 3. Co-occurring Conditions
15	**Dr LIAN Wee Bin** *Paediatrics and Neonatal Specialist* Medical Director SpecialKids Child Health & Development Clinic Singapore	Co-occurring Conditions	1. Complementary and Alternative Treatment 2. Co-occurring Conditions 3. Follow-up and Prognosis
16	**Dr LIM Hong Huay** *Director*, Rophi Clinic, *Board Member*, SG Enable *Board Chair and Project 3i Lead*, CaringSG		1. Caregiver and Family Support
17	**Prof Kenneth POON Kin Loong** *Associate Dean (Education Research)*, Office of Education Research; *Centre Director*, Centre for Research in Child Development; National Institute of Education, Nanyang Technological University		1. Intervention 2. Education and Transition 3. Professional Training
18	**Dr SIM Zi Lin** *Psychologist & Autism Therapist* Autism Resource Centre		1. Intervention 2. Education and Transition
19	**Dr SUNG Min** *Senior Consultant Psychiatrist* Department of Developmental Psychiatry, Institute of Mental Health	Pharmacological Treatment	1. Pharmacological Treatment 2. Co-occurring Conditions
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APPENDIX 2: AGREE-II RATINGS OF EXISTING CLINICAL GUIDELINES

Guideline Information				AGREE Scaled Domain Scores					
No.	Guideline Publisher	Guideline Title	Year	D1. Scope and Purpose	D2. Stakeholder Involvement	D3. Rigour of Development	D4. Clarity of Presentation	D5. Applicability	D6. Editorial Independence
Asia Pacific									
1	Cooperative Research Centre for Living with Autism (Autism CRC), Australia	A National Guideline for the Assessment and Diagnosis of Autism Spectrum Disorders in Australia	2018	91.7%	97.2%	93.8%	94.4%	97.9%	95.8%
2	Ministries of Health and Education, NZ	New Zealand ASD Guideline	2016			59.4%			
3	Ministry of Health, Malaysia	Clinical Practice Guidelines: Management of ASD in Children and Adolescents	2014			34.4%			
4	Indian Journal of Psychiatry	Clinical Practice Guidelines for ASDs	2019			2.1%			
UK									
5	National Institute for Health and Care Excellence (NICE), UK	Autism: Recognition, Referral and Diagnosis of Children and Young People on the Autism Spectrum (NICE CG128)	2017	100.0%	88.9%	93.8%	100.0%	68.8%	75.0%
6	National Institute for Health and Care Excellence (NICE), UK	The Management and Support of Children and Young People on the Autism Spectrum (CG170)	2013	97.2%	91.7%	89.6%	100.0%	70.8%	75.0%
7	Scottish Intercollegiate Guidelines Network (SIGN), UK	Assessment, Diagnosis and Interventions for ASDs: A National Clinical Guideline (SIGN145)	2016	88.9%	86.1%	76.0%	100.0%	83.3%	62.5%
8	British Psychological Society (BPS)	Working with Autism: Best Practice Guidelines for Psychologists	2021			26.0%			
9	British Association of Psychopharmacology (BAP)	ASD: Consensus Guidelines on Assessment, Treatment and Research	2017			25.0%			
Europe									
10	European Society for Child and Adolescent Psychiatry (ESCAP) ASD Working Party	ESCAP Practice Guidance for Autism: A Summary of Evidence-based Recommendations for Diagnosis and Treatment	2020			10.4%			
11	Autism Europe	People with ASD: Identification, Understanding, Intervention, 3rd Edition	2019			10.4%			

Guideline Information				AGREE Scaled Domain Scores					
No.	Guideline Publisher	Guideline Title	Year	D1. Scope and Purpose	D2. Stakeholder Involvement	D3. Rigour of Development	D4. Clarity of Presentation	D5. Applicability	D6. Editorial Independence
USA									
12	American Academy of Pediatrics (AAP)	Identification, Evaluation, and Management of Children with ASD	2020			12.5%			
13	American Academy of Child and Adolescent Psychiatry (AACAP)	Practice Parameter for the Assessment and Treatment of Children and Adolescents with ASD	2014			47.9%			
14	National Clearinghouse on Autism Evidence and Practice Review Team (NCAEP), Frank Porter Graham Child Development Institute	Evidence-Based Practices for Children, Youth, and Young Adults with Autism	2020	88.9%	13.9%	70.8%	55.6%	29.2%	50.0%
15	National Autism Centre, May Institute	Findings and Conclusions: National Standards Project Phase 2	2015			56.3%			
16	Missouri Autism Guidelines Initiative	ASDs: Guide to Evidence-based Interventions	2012			42.7%			
Canada									
17	Canadian Paediatric Society, Autism Spectrum Disorder Guidelines Task Force	Position Statements (x3) on Early Detection, Diagnostic Assessment and Follow-up Care	2019			19.8%			

APPENDIX 3: REFERRALS FOR AUTISM SPECIALIST SERVICES IN SINGAPORE

DIAGNOSTIC SERVICES

For preschool children (i.e., 6 years and below and not yet in Primary One):

KK Women's and Children's Hospital (KKH), Department of Child Development (DCD)

Tel: (65) 6394 1543/7216

Email: kkh.dcd@kkh.com.sg

Website: https://www.kkh.com.sg/patient-care/areas-of-care/childrens-services/Pages/child-development.aspx

or

National University Hospital (NUH) Child Development Unit (CDU) @ Jurong Medical Centre or Keat Hong

Tel: (65) 6665 2530 (Jurong Medical Centre) or 6769 4537 (Keat Hong)

Email: cdu@nuhs.edu.sg

Website: https://www.nuh.com.sg/our-services/Specialties/Paediatrics/Pages/Developmental-and-Behavioural-Paediatrics.aspx

For school-age children (i.e., Primary One and above):

Child Guidance Clinic @ Health Promotion Board or Sunrise Buangkok

Tel: (65) 6389 2200 (same number for both)

Website: www.imh.com.sg

INTERVENTION SERVICES

Intervention services are provided by the agencies above, and a comprehensive list of services for children and adolescents on the autism spectrum in Singapore is available at:

SG Enable

20 Lengkok Bahru (Enabling Village)

#01-01 Singapore 159053

Tel: 1800-8585-885

Email: contactus@sgenable.sg

Website: www.enablingguide.sg/service-directory

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