Autism 4

Evidence-based support for autistic people across the lifespan: maximising potential, minimising barriers, and optimising the person–environment fit

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This is the fourth in a Series of four papers about autism

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Autism is both a medical condition that gives rise to disability and an example of human variation that is characterised by neurological and cognitive differences. The goal of evidence-based intervention and support is to alleviate distress, improve adaptation, and promote wellbeing. Support should be collaborative, with autistic individuals, families, and service providers taking a shared decision-making approach to maximise the individual's potential, minimise barriers, and optimise the person–environment fit. Comprehensive, naturalistic early intervention with active caregiver involvement can facilitate early social communication, adaptive functioning, and cognitive development; targeted intervention can help to enhance social skills and aspects of cognition. Augmentative and alternative communication interventions show preliminary evidence of benefit in minimising communication barriers. Co-occurring health issues, such as epilepsy and other neurodevelopmental disorders, sleep problems, and mental health challenges, should be treated in a timely fashion. The creation of autism-friendly contexts is best achieved by supporting families, reducing stigma, enhancing peer understanding, promoting inclusion in education, the community, and at work, and through advocacy.

Introduction

Autism spectrum disorder (ASD) or autism spectrum conditions (ASC)[1,2]—referred to here as autism—are early-emerging neurodevelopmental conditions with strong genetic aetiologies,[3] shaped by gene–environment interplay.[4] Changing diagnostic criteria,[5] improved recognition of autism and its heterogeneous nature,[6] and increased awareness in society[7] mean that autism—formerly regarded as rare—is now deemed to be a relatively common condition. Globally, approximately 1% of the population has a formal diagnosis.[8] In high-income countries, the prevalence is close to 1·5%,[9] with a male-to-female ratio of about 3:1.[10] Characteristics associated with autism fall along a spectrum in the general population across dimensions of social communication, repetitive and stereotyped behaviours, sensory sensitivity, and other non-clinical and cognitive features (eg, attention to detail).[5] Autistic traits are particularly common in first-degree and second-degree relatives of people with an autism diagnosis, reflecting shared genetic background.[11] Both clinical autism and dimensional traits are associated with the additive effect of common and de novo rare genetic variations,[3,12] although the exact causal roles of associated variants remain unclear.

Autism affects an individual's development and ability to adapt across the lifespan (appendix p 1). Autistic people, even those who are diagnosed early in life, have variable long-term outcomes.[1] Many face everyday challenges in adaptive functioning throughout childhood, adolescence, and adulthood, including difficulties with independent living, education, employment, sexual and romantic relationships, community involvement, health, and quality of life.[1,2] An approach that acknowledges the dual nature of autism—encompassing both disabilities (resulting from atypical neurobiology) and differences (a neurodivergent profile of strengths and weaknesses)—is key to supporting autistic people (appendix p 3). In addition to the core characteristics of autism, many co-occurring health conditions—such as other neurodevelopmental disorders, epilepsy, sleep problems, and mental health challenges—are prevalent in autistic individuals.[1,2] Care should be multidisciplinary and collaborative, with shared decision making and action planning,[13] based on an in-depth understanding of the autistic individual's and the family's lived experiences.

In this Series paper, we aim to bring to the attention of health professionals from a variety of disciplines—including general practice, psychiatry, psychology, developmental paediatrics, and neurology—the best available evidence on existing interventions and support, and to highlight opportunities for progress in improving the health and wellbeing of autistic people. Despite decades of empirical research, evidence for treatment efficacy—even for some commonly used interventions[14]—is often weak or scarce. Nevertheless, the evidence base is improving, owing to more regular use of randomised controlled trial (RCT) designs, increasing focus on effectiveness and implementation,[14–16] and the incorporation of participatory research.[17] We propose a framework, based on current interventions, that comprises three pillars of evidence-based care and support across the lifespan: (1) maximising the potential of the individual by facilitating development and building skills; (2) minimising barriers that impede the individual's development and adaptation; and (3) optimising the person–environment fit by making reasonable environmental adjustments to enhance adaptation

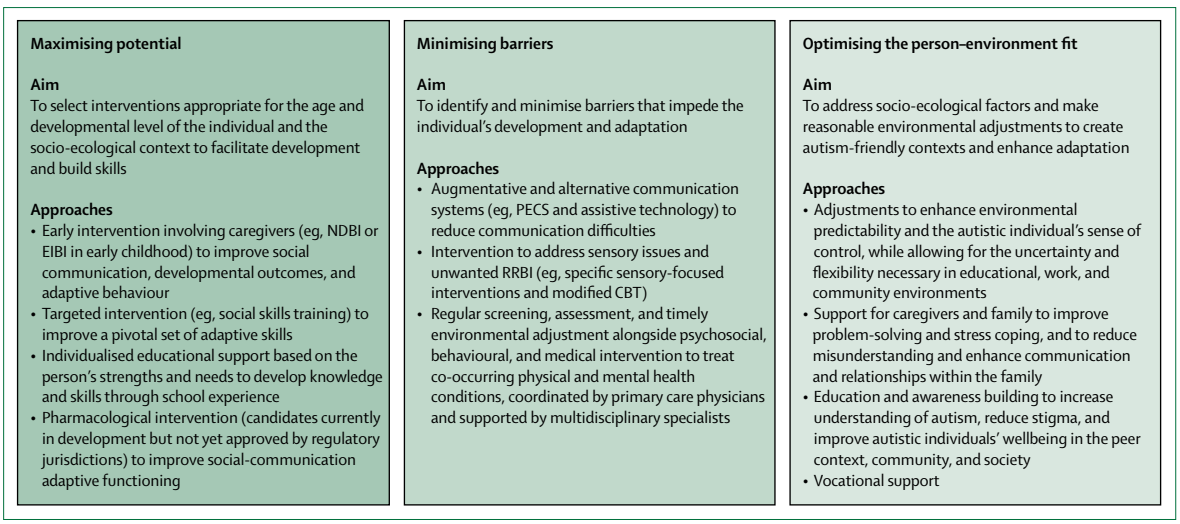

Figure 1: **A framework for the care and support of autistic people across the lifespan**
The proposed framework comprises three pillars based on available evidence-based interventions and promising new approaches to intervention and support. The overall goals are to enhance autistic people's adaptation and wellbeing and to reduce distress and disability. The framework could be adapted as novel evidence-based interventions become available. Complementary and alternative treatments with an acceptable safety profile (panel 4) could be incorporated on the basis of individual needs as the evidence base grows. CBT=cognitive behavioural therapy. EIBI=early intensive behavioural intervention. NDBI=naturalistic developmental behavioural intervention. PECS=Picture Exchange Communication System. RRBI=restricted, repetitive behaviour and interests.

(figure 1). Finally, we identify knowledge gaps and outline future directions for research. Although this Series paper focuses on autism, we hope that it provides a framework for the support of people with other developmental disabilities.

Meeting the needs of autistic people and their families

The dimensional nature of autistic traits makes it challenging to draw a clear diagnostic line, and this is likely to remain true even when other diagnostic biomarkers are available.[5] From a clinical perspective, a diagnosis is made on the basis of the intensity of autistic characteristics and the extent to which these characteristics cause impairment of adaptive functioning. This means that two people with the same level of autistic traits or the same underlying biomarkers can have different needs: one might benefit from a diagnosis because the traits affect their adaptive functioning, whereas the other might find that autistic traits do not impede their daily functioning and a diagnosis is not warranted. From a developmental perspective,[18] adaptation is the product of the transaction between an individual and their environmental contexts; a clinical diagnosis of autism is required only if there is a poor person–environment fit that results in impaired adaptive functioning.[2,4]

On the one hand, autism is a condition that entails disability, which requires treatment or intervention (the medical view). On the other hand, autism is a form of human variation, with a profile of strengths, differences, weaknesses, and disabilities that results in a lived experience that might fit comfortably or uncomfortably with a particular environment (the neurodiversity view). Polarising the medical and neurodiversity views, as if they were mutually exclusive, will hold back progress both scientifically and clinically. The duality view (appendix p 3) creates a common ground for medical, psychological, social, and environmental intervention and support for autistic people, with the aim of alleviating distress and improving adaptive functioning and quality of life (panel 1).[19–23]

Respecting the autistic individual's right to dignity and self-determination, while acknowledging disabilities, requires that as a society we create autism-friendly environments (similar to expectations for other developmental and physical disabilities). Support should be dynamic across the lifespan, as adaptation issues differ in childhood (eg, educational) versus adulthood (eg, residential and occupational). Transition to adulthood can be challenging and evidence-based support is insufficient at present.[24] Moreover, obtaining services and support for autistic adults, with or without communication or intellectual disabilities, has been particularly difficult owing to the structure of healthcare service systems and insufficient funding,[25] signalling a pressing need for systems-level improvement. Shared decision making among autistic individuals, families, and service providers should be at the heart of multidisciplinary, collaborative care (figure 2),[13] whether addressing the core disabilities of autism or co-occurring conditions. The lived experiences of autistic individuals and their families are central to understanding support needs, as shown by recent priority-setting initiatives (appendix p 5).[26–28]

International standards of evidence within medicine and health care have not been applied sufficiently, despite decades of empirical research on intervention and support

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See **Online** for appendix

Panel 1: **Principles for intervention and support in current clinical guidelines and recommendations**

Current clinical practice guidelines and recommendations developed by governmental or professional organisations rely on systematic reviews and expert panel discussions.[19–22] They commonly take a holistic approach and emphasise that service providers should do the following: (1) receive training in autism awareness and management, and ensure that the autistic individual and their family have access to health and social care services; (2) support the individual and family to obtain behavioural, educational, and psychosocial interventions (for children and adolescents) or vocational support (for adults), adjusted to the person's developmental level and individual needs to improve life skills, while acknowledging the level of evidence to date; (3) consider psychosocial, behavioural, and pharmacological treatment for co-existing challenges such as anxiety, irritability, hyperactivity-inattention, or sleep disturbances, based on knowledge derived from the autistic population when available, or from the non-autistic population; (4) facilitate adjustment of the social and physical environment and process of care to meet individual needs; (5) support families and carers; (6) maintain an active role in long-term support, including life transition issues (eg, transition to adult services); and (7) improve the involvement of autistic individuals and their families in planning of their own support. However, guidelines also vary in their recommendations regarding how social factors affect the diagnostic process, contexts of assessment, and interpretation of needs; further work is needed to improve clarity and consistency.[23]

for autism, as demonstrated by the latest rigorously conducted reviews.[14,29,30] The efficacy research literature is composed of more single-case designs than group designs of RCTs or quasi-experimental trials.[31] Most intervention trials are small in size—with a median sample size of 36, according to a 2018 survey[32]—and have a selection bias towards including a disproportionately small percentage of individuals with intellectual disability.[33] Few trials are able to show long-term benefits or generalisation of effects to wider contexts.[14] The result is generally weak or insufficient evidence for treatment efficacy, even for some commonly used early interventions and social skills groups.[14] It is troubling that many commercial interventions (ranging from behavioural to medical approaches) are widely advertised, actively promoted, and used by autistic people across the globe, but not supported by rigorous evidence. The evidence base for intervention and support in autism should not be exempt from the standards widely accepted in other fields of medicine.

An urgent need exists to improve the overall quality of evidence across all intervention and support approaches. We propose a framework for care and support, based on the evidence available for existing psychosocial, behavioural, biological, and environmental interventions, that could be adapted as understanding of the biological substrates of autism and co-occurring conditions progresses and new evidence-based interventions emerge (figure 1). Early diagnosis is the starting point for high-quality care and support (panel 2),[5] and key to successful outcomes for some interventions, but the proposed framework applies to autistic people across the lifespan. The characteristics and disabilities of people diagnosed later in life might seem to be subtle on the surface, but these autistic individuals still experience substantial challenges in adaptive functioning and threats to well-being that need to be addressed (panel 3).[2] A summary of current evidence for complementary and alternative treatments is provided in panel 4.[34–53]

Maximising potential

Early intervention

Early intervention generally refers to therapy for children aged 6 years or younger. Early intensive behavioural intervention (EIBI) has been widely used since the 1960s. The approach is based on applied behaviour analysis (ABA) principles and characterised by intensive (20–40 h per week) and long-term (1–4 years) intervention, use of discrete trial training, one-to-one delivery of teaching by an adult therapist, and comprehensive targets for improvements in skills and changes in behaviour. The latest Cochrane review,[54] based on a small number of trials—one RCT and four non-randomised controlled trials (a total of 219 children)—with a low quality of evidence, suggests that EIBI can improve autistic children's adaptive behaviour (mean differences [MD] on the Vineland Adaptive Behaviour Scale [VABS] composite, 9·58) and developmental outcomes, including intelligence quotient (MD 15·44), expressive language (standardised mean differences [SMD] 0·51), and receptive language (SMD 0·55); however, there was no significant effect of EIBI on core autism characteristics.

A US Agency for Healthcare Research and Quality (AHRQ) report[55] showed that models are moving away from structured (traditional EIBI) towards naturalistic approaches, under the umbrella term of naturalistic developmental behavioural intervention (NDBI).[56] Stimulated by research in developmental science and the cognitive science of autism, the development of NDBI models aims to reduce the discrepancy between highly structured ABA approaches and principles of child development (appendix p 8). However, NDBI is a broad category and not all models have been tested by rigorous RCTs or have equal levels of evidence, so positive findings from one NDBI model cannot be taken as evidence supporting another.

Evolving models recognise the importance of involving and training caregivers (panel 2). Parents act as co-therapists in several EIBI models, and caregiver involvement is core to NDBI given the emphasis on naturalistic social interaction and ecological validity (ie, representative of or generalisable to real-life situations).

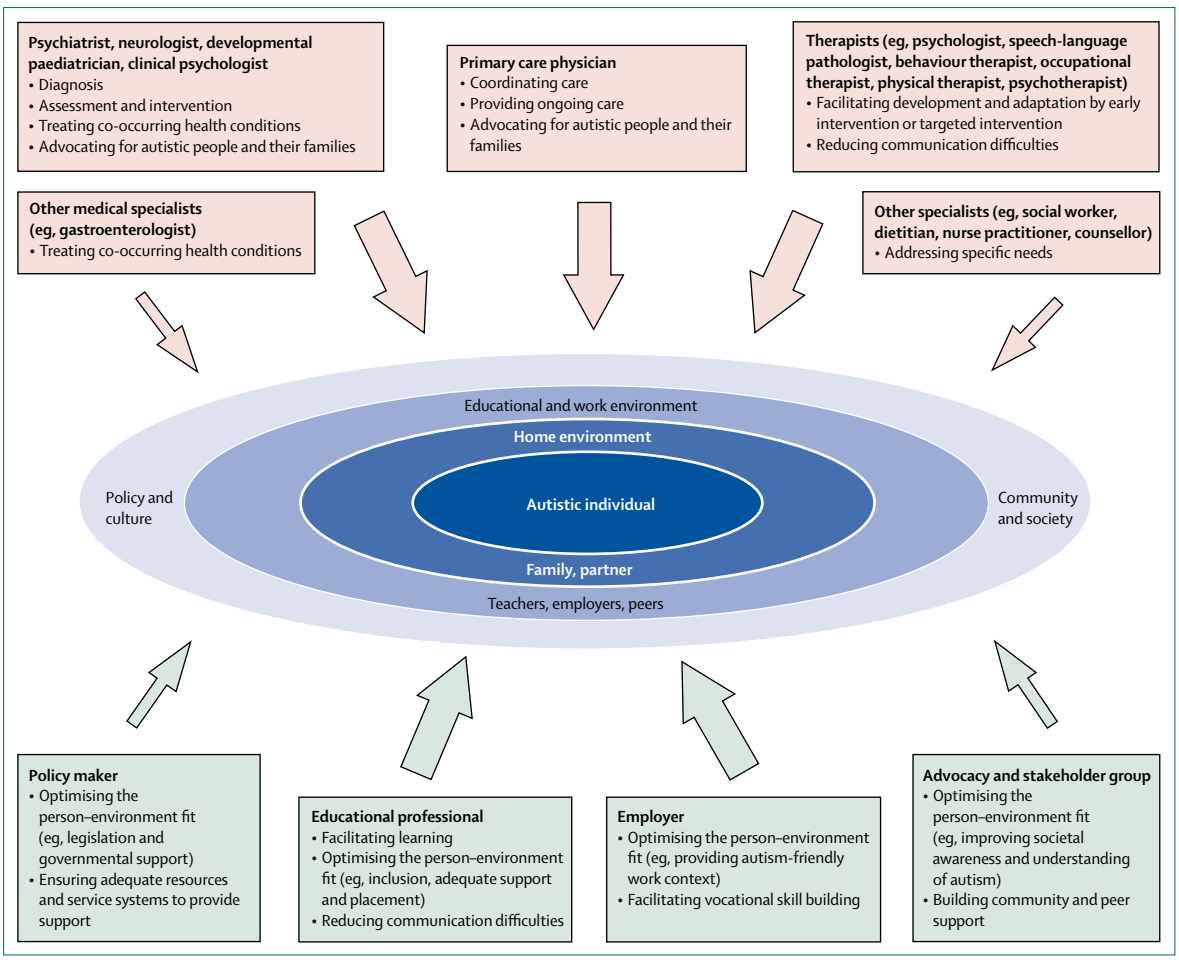

Figure 2: **Supporting autistic people across the lifespan through multidisciplinary care**
Adequate support for autistic people and their immediate environments (eg, home and family) involves multiple layers of socio-ecological contexts (blue) and requires coordinated, multidisciplinary care across health-care providers (red) and other professionals and parties (green), following the principles of shared decision making and collaborative action planning. Adequate service planning and care delivery should be shaped by consultations between professionals (eg, between primary care physicians and specialist clinicians). Advocacy from stakeholders and care providers is an ongoing work to drive systems-level change. Although each specialty is likely to have certain conventional roles in delivering care and support, we recommend that the three pillars (ie, maximising potential, minimising barriers, optimising the person–environment fit) should be the guiding principles for everyone providing care and support.

A rigorous systematic review of early-intervention RCTs showed that caregiver involvement was a part of many (34 of 48) tested models.[29] A meta-analysis including 19 RCTs published up to 2015 showed the benefit of parent-mediated intervention in reducing children's overall autism characteristics (Hedges' g=0·22; moderate quality of evidence), improving language communication and cognition (g=0·16 and g=0·24; moderate quality of evidence), and improving socialisation (g=0·22; very low quality of evidence).[57]

Rigorous trial methodology (eg, RCTs) needs to be used to adequately test the effectiveness of early interventions for autism.[14] The systematic review of 48 RCTs (Joint Attention Symbolic Play Engagement and Regulation [JASPER] was the most tested model) showed that, when overlooking performance bias (ie, lack of blinding of participants and relevant personnel) due to the nature of the interventions, only six studies (13%) met criteria for a low risk of bias.[29] Common biases include lack of blinding of outcome assessment and failure to specify a method of allocation concealment. Outcomes are positive in many trials, characterised by small effect sizes and wide confidence intervals; more studies are needed to clarify whether these small effects are sufficient to lead to positive distal outcomes. Major methodological challenges remain, including substantial heterogeneity and lack of consistency in sample characteristics, outcome measures, intervention models, and dosage (intensity and duration of intervention), insufficient understanding of effective subcomponents, mediators and moderators in most (often multicomponent) interventions, and scarcity of outcome measures that have proven sensitivity to change with intervention and are meaningful to autistic individuals and their families.[29,58] Effectiveness observed in

Panel 2: **Case study 1—early diagnosis and support**

JK was diagnosed with autism at 30 months of age. He showed limited sharing and eye contact when interacting with people, a lack of pointing to express interest, and no interest in playing with other children in day care. He spent long hours alone arranging toys by complex rules, with no symbolic or pretend play. He was very sensitive to the texture of clothing and ordinary noise, which easily triggered a meltdown. By 36 months, he spoke 10 single words with no phrases. JK's parents and paediatrician noticed his atypical development by 22 months and made a referral for a formal assessment. The paediatrician also suggested that the parents read an evidence-based book written for parents. The parents implemented the recommended strategies (eg, making use of JK's interests to increase his attention to people) in daily interaction at home even before the formal assessment.

After the diagnosis of autism, JK and his parents participated in an early-intervention programme that targeted joint attention, engagement, communication, and daily adaptative functions. The parents were trained by therapists via video-feedback to enhance their synchronisation with JK during daily activities. They found this particularly helpful compared with exploring strategies by reading books themselves. JK also received help from occupational therapists for sensory challenges. At 4 years old, he spoke only 20 words and used two idiosyncratic phrases for communication. Frequent frustration led to tantrums. After learning to use a tablet with communication software, the frequency of tantrums decreased. JK had an individual education plan at school. His health care was handled by his paediatrician and he saw a gastroenterologist for severe constipation, a neurologist for suspected absence seizures, and a child psychiatrist for extreme anxiety at the start of school. JK's parents were actively involved in a local parent-led group for autistic children, finding the support network useful and the advocacy work meaningful for themselves and many other families.

For more on **WHO's Caregiver Skills Training programme** see https://www.who.int/mental_health/maternal-child/PST/en/

community settings is lower than that reported in efficacy trials, reflecting gaps in implementation[59] and challenges to the external validity of efficacy trials (eg, poor generalisability due to biased enrolment).

Evidence from most rigorously conducted RCTs[29] indicates that naturalistic early interventions that focus on caregiver–child synchrony, joint attention, and engagement show positive changes in these proximal outcomes and (less reliably) in children's social-communication behaviour and autistic characteristics.[14] Caregiver-mediated intervention has also been extended to infants (12 months or younger)[29] who have an older autistic sibling[60] or show early signs of autism in community screening.[61] Prominent RCT-tested examples of interventions include the following: for infants with an elevated probability of developing autism, the adapted Video Interaction for Promoting Positive Parenting (iBASIS-VIPP);[60] and for toddlers and preschoolers diagnosed with autism, Video-feedback Intervention to Promote Positive Parenting adapted to Autism (VIPP-AUTI),[62] Preschool Autism Communication Therapy (PACT),[63] JASPER,[64] and potentially the Early Start Denver Model (ESDM),[65,66] Pivotal Response Treatment (PRT), and PRT derivatives.[67,68] Video-feedback based on recorded caregiver–child interaction seems to produce the most reliable changes to caregiver behaviour, in contrast to group or individual coaching and modelling;[14] however, these coaching methods have not yet been compared directly. Caregiver–child synchrony seems to be an important mediator of improvements in child social-communication behaviour in the caregiver–child dyad.[14] Long-term follow-up data from intervention studies show a reduction in objectively rated autism characteristics.[65,69,70]

Caregivers can also be trained via telemedicine or self-directed material.[71] Time-limited parent-mediated intervention has been found to be helpful for low-resource US families in improving preschoolers' joint engagement and initiation of joint attention,[72] showing promising accessibility. Effectiveness has also been demonstrated in different cultural contexts beyond European and North American countries.[73,74] To facilitate implementation worldwide, especially in low-resource communities, WHO has developed a Caregiver Skills Training programme to help caregivers to support children with developmental challenges, including autism. However, this programme needs to be tested for efficacy in different local contexts.[75] Development of resources and infrastructure to support and increase accessibility to caregiver-mediated early intervention is promising and should be further examined through healthcare service and implementation-science perspectives.

Targeted intervention

When autistic children approach school age (usually 5–18 years), educational support within and beyond the school system becomes a major source of intervention to facilitate independence and learning across daily living skills, academic skills, organisation and self-regulation, social interaction, and collaboration. This support is usually mandated by legislation in high-resource countries—but is inconsistent in other regions—and provided in various settings (eg, mainstream class, special education class, or through home-schooling) according to the child's needs and via a regularly updated individual education plan. For school-age autistic children, targeted intervention[31,76] designed to address a pivotal goal or set of skills with a fixed number of sessions can be helpful.[77]

The first category of targeted intervention focuses on enhancement of social skills and peer relationships. The latest meta-analyses showed that cognitively able autistic school-age children, adolescents, and adults benefit from group-based social skills training (the approaches most commonly tested in RCTs use the UCLA Programme for the Education and Enrichment of Relational Skills

[PEERS]), as shown by improved social skills and wellbeing.[78,79] However, the improvement varies by context and how performance is measured.[80] On the basis of 19 RCTs, there is a moderate overall improvement in social competence when all measures are aggregated (Hedges' *g*=0·51). The effects are largest when assessed via self-report (*g*=0·92), attributable to participants reporting having learned about social skills (social knowledge, *g*=1·15) rather than to perceived changes in their own social behaviour (social performance, *g*=0·28). Significant effects are larger for task-based measures (*g*=0·58) than for parent report (*g*=0·47) or observer report (*g*=0·40), but effects are non-significant for teacher report (*g*=0·41).[80] However, challenges remain in achieving actual social-behavioural changes, flexibility of social behaviour, and generalisability to different contexts outside the group setting and over time.[81]

A second category aims to enhance social cognition and social communication. A Cochrane review of 22 RCTs found that interventions for emotion recognition, joint attention, imitation, and mentalising had mixed outcomes in terms of changes in social, communication, and related cognitive skills, with low to very low quality of evidence.[82] Teaching facial-emotion recognition improves the recognition of static facial emotions (SMD 0·75); facilitating joint attention enhances joint engagement during parent–child play (SMD 0·55); and positive outcomes have been reported for approaches that target imitation and mentalising.[82] Consistent drawbacks include a lack of generalisation of the target skill to novel settings or when measured in more complex and new scenarios, with unknown long-term benefits. Joint-attention interventions for young children seem to have the most consistent positive effects in improving children's joint-attention initiation (Hedges' *g*=0·47) and response (*g*=0·93), with maintained effects (*g*=0·56)[83] and potential for distal generalisation to other aspects of social communication.[84] For RCTs of interventions that involve pragmatic language (including joint attention), a meta-analysis indicates an overall positive effect (*g*=0·50) not only in preschoolers (6 years or younger), but also in children aged 6–12 years; notably, group-based interventions and those involving typically developing peers appear to be more effective.[85]

The literature also shows preliminary positive outcomes for specific models, but more rigorous RCTs are needed to determine their efficacy. These models include the following: Social Stories (ie, a narrative written for an autistic individual that describes a social situation and expected behaviours) for social and play skills;[86] LEGO therapy (ie, leveraging the child's natural interest in LEGO to motivate behavioural changes in verbal and non-verbal communication, initiation, turn-taking, sharing, and collaboration) for social communication;[87] human–computer interaction technology (eg, computer, tablet, interactive DVD, and virtual reality) for emotion recognition and language, social, and academic skills;[88] and social robots for learning.[89] Many of these models do not require extrinsic rewards to capture the individual's attention because they harness autistic individuals' strengths and interests. This is in line with the principles of NDBI or of structured teaching models such as the Treatment and Education of Autistic and related Communication-Handicapped Children (TEACCH) programme.[90]

***Panel 3:* Case study 2—diagnosis in adolescence and transition to adulthood**

TC received her autism diagnosis at 16 years of age from a service specialised in mental health and autism. She had been diagnosed with generalised anxiety disorder at 6 years, attention deficit hyperactivity disorder at 8 years, and eating disorder at 14 years of age. She had used self-harm as a way to cope with distress. When an autism diagnosis was confirmed and explained to her by the child psychiatrist, she felt that it "made sense" in explaining her long-standing struggles with understanding social nuances, limited ability to engage in group conversations, need for a rigid day-to-day routine (including talking to her best friend at a specific time every day), and intense discomfort with tight clothing. She found thinking about her long-term challenges from the autism perspective a relief, as she could now see herself as different instead of "broken".

TC received coordinated care from a mental health team for transition-age youth (aged 15–29 years), including regular follow-ups with a psychiatrist, a consultation with a gynaecologist for premenstrual syndrome, modified cognitive behavioural therapy with a clinical psychologist to target emotion regulation and anxiety, a social skills programme for autistic teens and adults, and a support group led by autistic adults. She found learning about experiences from autistic peers (including reading books written by self-advocates) particularly helpful. She developed a major depressive episode a few months after a stressful transition to college. The depression remitted under psychiatric care, including antidepressant treatment. During follow-ups, she revealed to the team that she had also been questioning her gender since her early teens and increasingly felt the need to explore it further, even though this could be a source of conflict within her family. She was referred for support with a nurse practitioner in her primary care team and a social worker from a gender service team to cope with related health, identity, and family interaction issues.

Pharmacological interventions for core disabilities

No medications have been approved for core symptom domains that cause disabilities in autism in any regulatory jurisdiction so far. The selection of compounds for trials has been informed by potential translational targets emerging from genomics, neurobiology, and systems neuroscience.[14] Rapidly emerging findings suggest that identifying the biological underpinnings of various autism presentations is crucial to stratifying individuals for treatment, as per the principles of precision medicine.[6,91,92]

Panel 4: Evidence for complementary and alternative treatments

Complementary and alternative medicine or treatments are frequently pursued by autistic adults[34] and parents of autistic children.[35,36] Clinicians providing care to families should ask about the use of such treatments and be prepared to discuss their evidence base, risks, and benefits.[22,37] Overall, there is insufficient evidence of efficacy.[38] Some approaches show a potentially positive effect (eg, music therapy, massage, acupuncture, animal-assistance, exercise),[39] but others do not (eg, gluten-free and casein-free diets),[40] and some have substantial risks of harm (eg, chelation, hyperbaric oxygen therapy, and sex-hormone-inhibiting drugs such as leuprorelin).[41]

A Cochrane review found evidence (low-to-moderate quality) that music therapy (1 week to 7 months) can promote social interaction, verbal communication, initiating behaviour, social-emotional reciprocity, social adaptation, and parent–child relationship quality, even generalising to other contexts, and with no reported adverse effects;[42] but the latest and largest randomised controlled trial (RCT) failed to find an effect on autism characteristics after 5 months of improvisational music therapy.[43] A few trials with a high risk of bias showed that massage therapy might improve individuals' sensory profile, social communication, and adaptive behaviour during trial periods.[44] Acupuncture is not yet supported for altering autism characteristics, although some trials have shown reduced challenging behaviour and improved communication, social interaction, and cognitive or global functioning, with acceptable adverse events (very low quality of evidence and high heterogeneity of acupuncture methods).[45,46] Preliminary evidence exists for benefits of animal-assisted intervention (with therapy, service, or companion animals), although this approach needs to be tested in more rigorous trials.[47] A range of exercise interventions (eg, jogging, horseback riding, martial arts, yoga, dance, swimming, and weight bearing) tend to show benefits for motor, physical, behavioural, or cognitive outcomes.[48]

Evidence for nutritional and dietary intervention is limited: based on a low strength of evidence, omega-3 fatty acids do not reduce challenging behaviour or alter core autism characteristics;[49] findings for digestive enzymes, methyl-B12, levocarnitine, and gluten-free and casein-free diets are inconclusive and give insufficient evidence to support their use;[49] benefits, if reported, are often related to gastrointestinal (eg, food intolerance or malabsorption) or allergy (eg, grain allergy) issues; one RCT showed that folinic acid might improve verbal communication in children with autism and language impairment, especially in those positive for folate receptor-α autoantibody, but replication is needed.[50]

No supporting evidence exists for chelation and hyperbaric oxygen therapy, which have risks of serious adverse events.[51,52] No benefit has been found for secretin.[53]

Altered signal-to-noise ratio due to a neural excitation–inhibition imbalance has been proposed as a common biological feature in at least a subgroup of autistic individuals.[93] Studies of models based on specific genetic causes of autism—eg, fragile X syndrome[94] and 15q11-q13 duplication syndrome[95]—have documented changes in excitation–inhibition balance, although such alterations might be compensatory responses rather than a direct cause of autistic characteristics.[96] Attempts to manipulate the excitation–inhibition ratio have been made using drugs that target glutamate and GABA signalling. Memantine, an uncompetitive NMDA receptor antagonist approved for patients with dementia, did not change autistic characteristics in a large RCT (121 children aged 6–12 years), despite positive findings in previous smaller trials;[97] another RCT is ongoing (NCT01972074). However, D-cycloserine, a partial agonist of the glycine-binding site of the NMDA receptor, has shown some promise in augmenting social skills training at 22 weeks of treatment.[98] Two large RCTs of metabotropic glutamate receptor 5 (mGluR5) inhibitors did not show effects on social function, despite early promising human and animal studies.[99] The treatment of children younger than 12 years has not been evaluated adequately with these compounds. Early studies show mixed results for riluzole, a compound affecting both presynaptic and postsynaptic glutamatergic transmission and glutamate release from glia, previously approved for the treatment of amyotrophic lateral sclerosis, with an RCT in autistic children and adolescents ongoing (NCT01661855). Conversely, GABAergic manipulation has been attempted with arbaclofen, the *R*-enantiomer of baclofen and a $GABA_B$ receptor agonist. An RCT was negative for social withdrawal,[100] but secondary analysis showed positive effects on socialisation measured by the VABS; two phase 2 RCTs are currently ongoing (NCT03682978 and NCT03887676). Changes in neural excitation–inhibition balance and subsequently long-term potentiation and depression as plausible physiological underpinnings of autism imply that future successful intervention would probably require the combination of compounds targeting such pathways and concurrent behavioural and learning interventions.

Receptors for oxytocin and vasopressin, and the downstream effects of receptor activation, are plausible targets of pharmacological interventions for autistic individuals' core social communication difficulties because these neuropeptides are involved in social perception and cognition across species. Results for oxytocin treatment have been mixed so far.[101] A major limitation is that the only available delivery mode in humans is intranasal, but drug absorption and distribution to the brain is still not well established. A small pilot RCT showed some promise for social cognition and social-emotional wellbeing,[102] but findings in follow-up RCTs have been inconsistent.[103–106] The long-term efficacy of oxytocin administration is equivocal.[107] Potential benefits, if they exist, might be contingent on a personalised design, considering the developmental stage, contextual factors, neurobiological characteristics including sex, and adjuvant intervention.[108] Several larger RCTs of oxytocin and vasopressin are ongoing (eg, NCT01944046, NCT01788072, NCT01962870, and NCT02901431). A phase 3 RCT of balovaptan, a vasopressin V1a receptor antagonist, in autistic adults (NCT03504917) is ongoing in North America and Europe, following a phase 2 RCT that showed improved social-communication adaptive functioning in autistic men;[109] a phase 2 RCT in children and adolescents is also currently ongoing (NCT02901431). RCTs that combine promising compounds with social-learning interventions (eg, NCT02918864) are needed.

Altered serotonin mechanisms and increased serotonin blood concentrations have been reported in subgroups of autistic people; interactions between serotonin and other neuropeptides, including oxytocin, might be particularly

important for social behaviour.[110] A large RCT of buspirone in children aged 2–6 years showed no difference in the Autism Diagnostic Observation Schedule total score, but it did show a reduction in the restricted and repetitive behaviour score, on 2·5 mg twice daily.[111] This finding needs to be replicated, and whether the effect can be further enhanced with concomitant behavioural intervention is unclear.

Four large-scale medication RCTs (NCT02901431, NCT03504917, NCT03682978, and NCT03887676) are currently focussing on adaptive functioning as a primary outcome (eg, social-communication adaptive functioning measured by the VABS). This choice of primary outcome measure reflects increasing appreciation that the primary goal of pharmacological interventions is to enhance adaptation and wellbeing associated with core autistic characteristics.

Minimising barriers

Reducing communication difficulties

Enhancing verbal and non-verbal communication is core to many early interventions. Despite such interventions, some autistic children produce little expressive (spoken) language by 5 years of age. Helping minimally verbal children[112]—about 30% of all autistic children—requires skilled assessment and recognition of strengths. These children often show floor effects on standardised direct assessments across domains, which could mean that true cognitive potential is underestimated.[113] New assessments are in development to understand the unique cognitive profiles of minimally verbal children, especially in the non-verbal domains.[112] Preliminary evidence suggests that including augmentative and alternative communication systems (eg, devices for non-speech means of expressive and receptive communication) might lead to better outcomes across domains for early interventions.[114,115] However, the RCT literature on communication interventions for minimally verbal individuals is generally limited.[116] Future research should thus incorporate appropriate measures and investigate various communication outcomes.

The manualised Picture Exchange Communication System (PECS) trains the minimally verbal child to use specific pictures for request and commentary as a means of functional communication. Teaching communication with PECS training increases autistic children's functional communication using this system, and neither inhibits nor facilitates spoken language development.[117] The use of speech-generating devices (eg, mobile devices with communication applications) is superior to PECS or manual sign language for minimally verbal autistic individuals in increasing their requesting repertoire, although the effects on non-requesting functional communication and spoken language remain unclear.[118] Two RCTs show that incorporating speech-generating devices into JASPER plus Enhanced Milieu Teaching increases spontaneous verbal (spoken) communication beyond requesting and communication interchanges in school-age minimally verbal autistic children.[119,120]

Assistive technology minimises communication barriers for minimally verbal autistic individuals, and helps verbal autistic individuals to overcome challenges in daily social-communication scenarios.[121,122] Although the precise benefits and drawbacks of incorporating augmentative and alternative communication in early interventions or targeted interventions are unclear,[114] advancing technology has potential in minimising barriers for learning and development, and should be included in future trials.[123]

Coping with sensory experiences and RRBI

Some sensory characteristics can be soothing for autistic individuals (eg, sensory interests), whereas others might be challenging (eg, in the case of hyper-responsivity). The function of sensory behaviours in young children is still largely underexplored. Hyper-responsivity might be especially associated with anxiety.[124] Alleviating sensory-related challenges has been a focus of occupational therapy, based on a combination of theoretical approaches. An AHRQ systematic review of 24 studies (20 RCTs) found limited, potentially short-term (less than 6 months) benefits for specific approaches, with a low strength of evidence:[125] sensory integration improved measures related to sensory and motor skills; environmental enrichment (sensory stimulation to promote tolerance) improved non-verbal cognitive skills; massage improved autistic symptoms and sensory challenges; but approaches based on auditory integration did not improve language. More sensory-related research in autism is needed to develop rigorously tested interventions tailored to the multidimensional, multimodal sensory characteristics of autistic individuals.[126]

Some restricted, repetitive behaviour and interests (RRBI) might need intervention. Many egosyntonic (ie, acceptable to oneself) RRBI can be soothing, anxiety relieving, and self-regulating, or a reflection of the individual's learning style;[127,128] others might be challenging if they contravene social-contextual expectations or interfere with the individual's adaptation. Understanding the function of RRBI is essential. Problematic RRBI might attenuate when social communication is facilitated or stress level reduced.[129] For autistic adults who have narrow interests, motivation for engaging in interests is associated with increased subjective wellbeing, but long engagement durations are associated with poor wellbeing,[130] which highlights the importance of optimal engagement. RRBI and their plausible cognitive bases (eg, focused attention, attention to detail, hyper-systemising, and weak central coherence) have the potential to support social communication and an individual's sense of personal achievement.[131,132]

Too few studies treat RRBI as the primary outcome,[133] and insufficient evidence exists for a reduction in RRBI by psychosocial interventions (see the UK National Institute for Health and Care Excellence [NICE] guidance on

For **guidance on support and management for autism** see https://www.nice.org.uk/guidance/cg170

support and management for children and young people with autism) or medications.[134] The effect of selective serotonin-reuptake inhibitors (SSRIs) on interfering RRBI or co-occurring egodystonic (ie, repugnant, distressing) obsessive compulsive disorder (OCD) symptoms is not yet established (eg, potential benefits are reported for adults but not children) and deserves further investigation.[134] Preliminary studies suggest that modified cognitive behavioural therapy is a promising approach.[135] Although trials of risperidone and aripiprazole showed a small reduction in RRBI as a secondary outcome,[136,137] risk of harm must be carefully weighed against benefits in clinical decision making.

Treating co-occurring health conditions

For **guidance on the diagnosis and management of epilepsy** see https://www.nice.org.uk/guidance/CG137

Autistic individuals are more likely than non-autistic members of the general population to have several closely linked health conditions,[138–141] probably because of shared causes and biological mechanisms, or as a result of experiences of living with autism (panels 2 and 3).[76,142] Common co-occurring neurodevelopmental challenges include intellectual disabilities, language disorders, attention deficit hyperactivity disorder (ADHD), tic disorders, learning disorders, and genetic anomalies;[141,142] medical conditions include epilepsy, immunological disorders, gastrointestinal disorders, and sleep problems;[138–140] mental health issues include anxiety, depression, OCD, irritability, self-injurious behaviour, suicidal risk, bipolar disorders, and psychotic disorders.[76,141,143] Impaired emotion regulation, possibly associated with the atypical neurobiology of autism and the absence of autism-friendly environments, might at times—and with consideration of family psychiatric history—be a more parsimonious explanation of co-occurring conditions than isolated multiple psychiatric diagnoses.[144] As a general principle, proper evaluation of potential environmental triggers and psychosocial or physical stressors is the first step in evaluating behavioural difficulties and psychiatric presentations (eg, irritability, hyperactivity, anxiety, and sleep disturbances).[145–148]

For **primary care resources** see https://autismandhealth.org

Co-occurring health conditions have negative impacts on wellbeing[149] and can increase mortality risk.[150] Autistic people need primary care providers who understand autism and the associated cognitive, communication, and social issues, can identify co-occurring health conditions and potential complications (eg, obesity), help with decision making, identify when violence and abuse is directed towards the individual, and make referrals to specialists.[151,152] While child neurologists, child psychiatrists, and developmental paediatricians are usually comfortable working with the autistic population, a plan should be in place for a smooth transition to adult providers and specialists at an appropriate age.[151,153]

In current practice, there is considerable use (and risk of overuse) of psychotropics in the autistic population, especially antipsychotics, stimulants, antidepressants, and their combinations, with a median prevalence of 45·7%.[154,155] However, evidence-based guidelines for the treatment of co-occurring conditions in autism are often unavailable. In such scenarios, clinicians should follow guidelines developed for the general population and modify care based on individual needs. An extensive discussion of specific treatments can be found elsewhere.[15,30,143,156]

Several guidelines and recommendations suggest routine clinical genetic testing (ie, chromosome microarray, G-banded karyotyping, and fragile X syndrome testing),[157,158] even exome sequencing[159] or whole-genome sequencing in the foreseeable future.[160] Results inform the surveillance of health issues and genetic counselling, with the potential to lead to precision medicine.[142,156]

Assessment and treatment of epilepsy and other medical conditions should follow best practice in the general population (eg, NICE guidance on the diagnosis and management of epilepsy). Evaluation of gastrointestinal problems should be thorough and in line with standard practice, especially noting that so-called problem or challenging behaviour might be the primary manifestation of medical causes.[161] Assessment of sleep problems should include medical contributors and sleep hygiene; when behavioural approaches fail, melatonin can be considered.[143,148]

Managing irritability and so-called problem or challenging behaviour must start by eliminating potential contributors (appendix p 26).[145] Behavioural parent interventions show efficacy in reducing autistic children's disruptive behaviour and hyperactivity, and parent stress.[162] If such interventions are insufficient, add-on pharmacological interventions could be considered: aripiprazole or risperidone at the lowest effective dose in high-risk to safety or loss of educational placement scenarios (based on established evidence from multiple RCTs, but with substantial risk of persistent adverse effects),[163] and clonidine or *N*-acetylcysteine in low-risk scenarios (based on preliminary evidence from single pilot trials and with low evidence of associated harms).[145,164] If long-term use of aripiprazole or risperidone is indicated, side-effects (eg, somnolence, weight gain, metabolic syndrome, and extrapyramidal symptoms) must be monitored and managed.[165] An RCT suggests that metformin has a modest effect in decreasing weight gain associated with the use of atypical antipsychotics.[166]

ADHD symptoms, particularly hyperactivity, can be treated with methylphenidate (and potentially other stimulants), atomoxetine, or guanfacine (and potentially clonidine), supported by RCTs,[143,146] but side-effects (eg, anxiety) might be more frequent or severe than in individuals with ADHD without autism.[143] Modified cognitive behavioural therapy shows promise in reducing anxiety in autistic people.[167] Although SSRIs and other antidepressants have been shown to reduce anxiety in non-autistic populations of different ages, insufficient evidence exists for efficacy in reducing autism-related anxiety (eg, fear of uncertainty or change, or sensory overload). It is possible that SSRIs

and other antidepressants could reduce typical anxiety in autistic individuals, as in the non-autistic population (eg, generalised or social anxiety), especially in those with a positive family history of anxiety disorders, but further investigation is needed. When prescribing SSRIs, clinicians should start with a low dose, exercise caution in increasing the dosage, and watch for the higher risk of behavioural activation (eg, increased energy and activity, impulsivity, irritability, disinhibition, and insomnia).[147]

Increased suicide risk has been reported in autistic adolescents and adults across different countries and should be assessed with a view to intervention.[168] Self-injurious behaviours are not uncommon and can be persistent, especially in those with intellectual disabilities, and might be associated with higher levels of stereotyped behaviour, impulsivity, sleep disorder, anxiety, and atypical pain processing.[169] For catatonia, early-stage treatment is important because chronic catatonia is more difficult to manage; electroconvulsive therapy, high-dose lorazepam, and behavioural interventions might have short-term benefits, based on studies with single-case designs and case series (extremely limited evidence).[170] Adolescents with first-episode psychosis and underlying autism are less likely to have a beneficial response to antipsychotics compared with those without autism.[171] Overall, insufficient evidence exists to guide the pharmacological treatment of depression, OCD, or psychotic or bipolar disorders in autistic people, despite the greater occurrence of these conditions in the autistic population.[141]

Few RCTs have focused on the health concerns of transition-age autistic youth and adults. Clinical decisions are often made on the basis of a clinician's experience and extrapolation from evidence in autistic children or in non-autistic individuals. Until there is evidence that pharmacological treatment should be different, a similar decision-making process as in the general population should be considered best practice. However, as in the wider population of people with developmental disabilities, a higher sensitivity to adverse effects of psychotropic medications might be expected.[155] They should be prescribed with caution and with clear targets: start low, go slow, watch for behavioural activation and side-effects.

Prospective, longitudinal studies examining the risk and protective factors for health issues across the lifespan are needed. Studies suggest that within-family (parental) stress[172,173] and autistic individuals' adverse experiences (eg, bullying or being rejected)[174,175] predict poorer health and functional outcomes. Enhancing the individual's ability to cope with stress and reducing unhelpful stress load is integral to minimising health challenges and improving resilience.[176] Preliminary data indicate that mindfulness-based interventions might reduce anxiety, depression, and rumination, and enhance wellbeing in autistic individuals of different ages,[177] but the evidence is insufficient owing to a lack of rigorously conducted RCTs.

Optimising the person–environment fit

Supporting autistic individuals must go beyond the individual to address socio-ecological factors.[176] The idea of optimising the person–environment fit by creating autism-friendly contexts[2] comes from the concept of promoting goodness-of-fit between parental expectations and children's temperaments (eg, guiding parents to recognise and make appropriate adjustment according to children's temperaments) from Chess and Thomas,[178] and has been included in some existing approaches: TEACCH aims to enhance learning by structuring the environment on the basis of autistic individuals' strengths and weaknesses;[132] caregiver-mediated early interventions involve adjusting the environment to increase children's initiative[56] and enhance parent responsivity and caregiver–child interaction synchrony.[63] Optimising the person–environment fit entails enhancing the autistic person's sense of control and environmental predictability, while allowing for uncertainty and flexibility that is necessary in educational, work, and community environments. This should be an a-priori consideration for all support and intervention.

Care for families of autistic individuals is essential, as family often provides the immediate microenvironment supporting individual development (figure 2). In general, caregiver-mediated skill-building interventions for autistic children show a positive secondary impact on family functioning and relationships.[179] Although the evidence for direct family (systemic) intervention to enhance communication, relationships, or coping is lacking,[180] clinicians should aim to work with autistic individuals and families to find the balance between reasonable environmental adjustment and opportunities for flexibility and exposure that are manageable for the individual. This is a dynamic, long-term process. Hence, supporting families is as important as supporting the autistic individual. Preliminary evidence shows promise for the effectiveness of mindfulness-based stress reduction, positive psychology approaches, and problem-solving education for parents of autistic individuals in reducing their own stress, anxiety, and depression.[181–183] Future studies need to identify the effective components of family-systems-oriented support and how the wellbeing of all parties can be improved, especially by reducing misunderstanding[184] and enhancing communication and coherence. How personal characteristics of family members (including levels of autistic traits) can be taken into account and leveraged to enhance the person–environment fit, during caregiver-mediated early interventions or family-systems approaches across the lifespan, should be tackled in future clinical research.

Peer influence is particularly related to the wellbeing of autistic children and youth. Inclusion and appropriate placement in education is essential but still a largely unmet need, primarily owing to inadequate or unhelpful attitudes and practice in educational contexts rather than insufficient formal regulations.[185] Non-autistic adults often have a negative first impression of autistic adults, which is

	Aims and considerations	Available approaches (source of best evidence)*	Goals of future research
Maximising potential			
General	Overall aim to facilitate development and build skills, in order to enhance adaptation and wellbeing; clinicians should discuss with autistic individuals, families, and other stakeholders whether target behaviour needs intervention or is better understood as part of neurodiversity	..	New skill-building models that harness autistic individuals' cognitive strengths; biological interventions that facilitate skill building and development; outcomes that are meaningful to autistic individuals and families; outcomes that are sensitive to change with intervention; new intervention models that harness individuals' strengths for learning and adaptation
Early intervention	Enhancement of early person–environment fit (eg, caregiver–child synchrony) is key to good outcomes; selection of intervention target and method should consider child's learning pattern (eg, cognitive strengths and weaknesses) with emphasis on intrinsic rewards for learning; long-term impact and potential adverse effects should be examined for current and future interventions	Comprehensive, naturalistic interventions that actively involve caregivers for children aged ≤6 years:[29] iBASIS-VIPP,[60] VIPP-AUTI,[62] PACT,[63] JASPER,[64] and possibly ESDM,[65,66] PRT, and PRT derivatives[67,68] (RCT, systematic review, meta-analysis, and evidence-based practice guideline)	Biological interventions that facilitate skill building and development when combined with early behavioural interventions; individualised caregiver-mediated interventions that consider caregivers' personal characteristics (including autistic traits) and other contextual factors
Targeted intervention	Intervention should consider autistic individuals' best interests and take into account developmental level, social capacity, stress coping, and social preference	Age-appropriate, group-based social skills training (eg, PEERS)[78,79] and intervention focusing on joint attention, emotion recognition, imitation, mentalising, and pragmatic language[82,85] for individuals aged ≥6 years (RCT, systematic review, meta-analysis, and evidence-based practice guideline)	Modification of intervention to achieve lasting social behavioural changes, flexibility of behaviour, and generalisability to different contexts; new cognition-enhancing and skill-building models that go beyond the social cognitive domain to also address executive dysfunction
Minimising barriers			
General	Overall aim to identify and mitigate barriers to adaptation and development; clinicians should discuss with stakeholders whether target behaviour needs intervention	..	New medical, technological, and environmental approaches to mitigate barriers
Reducing communication (including language) difficulties	Challenging behaviour might stem from communication barriers; communication opportunities should be explored with autistic individuals and families (alert to untrustworthy or exaggerated claims of success), with respect for individuals' preferred means of communication	AAC systems to reduce communication barriers in minimally verbal individuals;[114,115] effectiveness not established[116] (RCT, systematic review)	Methods of cognitive assessment tailored to establish true abilities of minimally verbal individuals; RCTs that examine adjuvant effects of AAC systems with existing early comprehensive or targeted interventions
Coping with sensory experiences and RRBI	Egosyntonic RRBI at different developmental levels, either behavioural (eg, repetitive movement or speech) or cognitive (eg, narrow interests or preoccupation), might reflect autistic individuals' learning styles or positive ways of coping	Sensory-focused intervention for sensory-related outcomes;[125] modified CBT to reduce egodystonic RRBI or OCD symptoms;[135] effectiveness not established[133] (RCT, systematic review)	New interventions to reduce functionally impairing or egodystonic repetitive or obsessive-compulsive behaviour and inflexibility, tested in RCTs; interventions to alleviate sensory-related challenges, tailored to multidimensional, multimodal sensory characteristics in autism
Treating co-occurring health conditions	Challenging behaviour or psychiatric presentation might reflect poor person–environment fit or experiences of living with autism; mental health challenges require careful assessment and treatment, and might be reduced by environmental adjustments	Regular screening, assessment, and timely treatment of health issues across the lifespan, coordinated by primary care physicians and supported by multidisciplinary specialists;[22,30,143,145–148,156] see main text for details (RCT, systematic review, meta-analysis, and evidence-based practice guideline)	Understanding of biological and experiential causes of co-occurring physical and mental health challenges in autistic people; new targeted (autism-informed) treatments; coordinated models of timely health care for autistic people across life stages, with improved accessibility to health care and flexibility to scale up and modify according to local contexts

AAC=augmentative and alternative communication. CBT=cognitive behavioural therapy. ESDM=Early Start Denver Model. iBASIS-VIPP=adapted Video Interaction for Promoting Positive Parenting. JASPER=Joint Attention Symbolic Play Engagement and Regulation. OCD=obsessive compulsive disorder. PACT=Preschool Autism Communication Therapy. PEERS=Programme for the Education and Enrichment of Relational Skills. PRT=Pivotal Response Treatment. RCT=randomised controlled trial. RRBI=restricted, repetitive behaviour and interests. VIPP-AUTI=Video-feedback Intervention to Promote Positive Parenting adapted to Autism. *Quality of evidence based on resources reviewed in this paper and criteria used by the included systematic reviews and meta-analyses (eg, Grading of Recommendations, Assessment, Development and Evaluations); see main text for details.

Table 1: **Current best evidence, considerations based on the duality framework, and future directions for approaches to maximise potential and minimise barriers**

associated with reduced motivation to pursue social interaction with them.[186] However, better understanding of autism is associated with more positive impressions of autistic individuals among their non-autistic peers.[187] Thus, improving autism knowledge among non-autistic peers might improve the social wellbeing of autistic individuals. Preliminary evidence shows that school-based, peer-mediated interventions (eg, teaching peers autism knowledge and skills to support autistic individuals)[188,189] and sibling involvement in interventions[190] lead to better functioning of autistic individuals. Social-engagement intervention in the school playground (eg, the Remaking Recess programme) also increases the interaction between autistic children and their peers.[191] Novel RCTs that target both autistic individuals and neurotypical peers are starting to establish evidence for interventions that focus on the person–environment fit (eg, NCT03785327).

Preparing for and finding appropriate employment is essential but challenging for transition-age youth and adults. Improving vocational success has inclusion and

economic benefits for autistic individuals and society.[192] To enhance occupational success, supported employment (eg, community placement and job coaching) and technology-based or media-based support tools (eg, videotaped modelling of work behaviour) are potentially beneficial.[193] Existing interventions focus mainly on modifying the behaviours of autistic individuals for improved job performance, but insufficiently consider the impact of environmental barriers and facilitators.[194] Vocational success does not depend solely on skill building of the autistic person, but is also linked to community resources, family support, workplace capacity building—the Ready, Willing and Able partnership is an example of the support available to build an inclusive workforce—advocacy, and policy.[195] Initiatives that use an ecosystem approach via private–public partnerships are developing—examples include Worktopia and the Autism@Work employer roundtable—but there is still an urgent need for new interventions (and empirical evidence) that target the environment.[194]

Autistic individuals and their families tend to experience stigma, which substantially contributes to life difficulties.[196,197] Stigmatisation can also be promoted through the media.[198] Programmes that aim to reduce the stigma associated with autism, implemented in the school setting[199] or through the media (eg, the Sesame Street and Autism initiative), are promising, but evidence of their effectiveness needs to be established in future studies.

	Aims and considerations	Available approaches (source of best evidence)*	Goals of future research
General	Overall aim to address socio-ecological factors and make environmental adjustments to create autism-friendly contexts and enhance adaptation; an a-priori consideration for all interventions	..	RCTs that concurrently target the autistic individual and family, and peer, school, work, and societal contexts; lifespan support for transition to adulthood and healthy ageing; approaches that can be scaled up to have impact at the systems level
Supporting caregivers and family	An iterative process should be adopted to identify the need for and make reasonable environmental adjustments, and to reduce misunderstanding and enhance communication and coherence within the family	Mindfulness-based stress reduction, positive psychology, and problem-solving approaches;[181–183] effectiveness of family therapy not established[180] (RCT, systematic review)	Interventions that target the family as a system (eg, family relationships, intimate and romantic relationships); caregiver-mediated early interventions or family-systems approaches across the lifespan that consider personal characteristics of family members (including autistic traits)
Improving the peer environment	Inclusion and appropriate placement in education, workplace, and community depends on improvement in peers' understanding of autism and autistic people	School-based, peer-mediated interventions;[188,189,191] effectiveness not established (RCT, systematic review, and meta-analysis)	School-based and workplace-based, peer-mediated intervention and support
Enhancing vocational success	Autism-friendly physical and social environments should be created; approaches should harness autistic individuals' strengths to identify best fit	Supported employment and technology-based or media-based support tools;[193] effectiveness not established (systematic review)	Evidence-based interventions that target job contexts and work environments

RCT=randomised controlled trial. *Quality of evidence based on resources reviewed in this paper; see main text for details.

Table 2: **Current best evidence, considerations based on the duality framework, and future directions for approaches to optimise the person–environment fit**

Conclusions and future directions

The duality of autism should not be viewed as opposing perspectives—a disorder to be treated or a variant of human nature to be cherished. When both the identity and disability of autism are recognised and embraced,[200] it becomes clear that enhancing adaptation and wellbeing is the common ground and ultimate goal for any support and intervention. To meet this goal, collaborations among autistic individuals, families, service providers, policy makers, and advocacy groups, targeting both autistic individuals and environmental contexts, are needed.

Of the three pillars of support that we have described (figure 1), most evidence is available for specific models of naturalistic early intervention that actively involve caregivers, targeted interventions for the building of social skills, and specific treatments for co-occurring mental health challenges. However, the knowledge gaps that need to be filled are currently more substantial than the established evidence (tables 1, 2). Here, we outline five overarching directions for future research.

First, participatory research that involves autistic people and their parents or caregivers in the design of interventions should be widely adopted.[17] This partnership is central to identifying meaningful targets, intervention content, ways of delivery, and relevant outcomes beyond conventional symptom, cognitive, or functional measures.[201] The intervention literature lacks novel models that focus on both the autistic individual and contextual factors (ie, family, peer, school, work, and societal contexts), and their interactions. Participatory research could be especially informative in this respect.

Second, autism intervention research needs to include well powered, robustly designed RCTs to examine both benefits and harms of existing and future interventions across all three pillars of support, taking into account what effects should be reasonably expected effects considering the nature of the intervention (eg, behavioural *vs* pharmacological, and short-term *vs* long-term) and the heterogeneity of participants.[6] These RCTs ideally should provide information about mechanisms of intervention effects and generalisability across functional domains and environmental contexts, and include a longitudinal component to understand long-term outcome and developmental trajectory.[14]

Third, because of the substantial clinical, biological, and aetiological heterogeneity of autism,[6] a one-size-fits-all intervention is unlikely to exist. Moving towards precision medicine, the age-old question of what works for whom can be answered only by clarifying heterogeneity in autism via multi-level stratification approaches[6]

For more on the **Ready, Willing and Able partnership** see http://readywillingable.ca/

For more on **Worktopia** see https://worktopia.ca/

For more on the **Autism@Work employer roundtable** see https://disabilityin.org/what-we-do/committees/autism-at-work-roundtable/

For more on the **Sesame Street and Autism initiative** see http://autism.sesamestreet.org/

Search strategy and selection criteria

We searched PubMed for systematic reviews, meta-analyses, guidelines, and other reviews published in English from Jan 1, 2000, to Sept 30, 2019, using the search terms "autis* AND (intervention OR treatment)". We supplemented our list of publications by searching the reference lists of identified reviews and performed more focused searches for relevant empirical research publications specific to the domains discussed in this Series paper. For our review of pharmacological interventions, we also searched for medication trials registered at the US National Library of Medicine database (ClinicalTrials.gov), using the search term "autism" with specification of "clinical trials" as study type, "medication" as intervention, and including phase 2, 3, and 4 trials. We also performed a search in the Cochrane Database of Systematic Reviews for any systematic reviews and meta-analyses relating to autism and summarised the findings in the appendix (p 12). The final reference list was generated on the basis of relevance to the topics covered in this Series paper, with the aim of synthesising the most up-to-date empirical findings and identifying challenges that remain with regard to support and intervention.

and adaptive trial methods that tailor to individual characteristics and treatment responses (eg, the Sequential Multiple Assignment Randomised Treatment [SMART] design; appendix p 27).[119,202] New interventions for subgroups with specific mechanisms can then be tested in a more targeted way.

Fourth, for evidence to be translated into the real world, effectiveness and implementation trials are necessary to test how the models can be tailored to unique local contexts, and be scaled up and made accessible. This crucial evidence can then form the basis of useful clinical guidelines that adequately consider social contexts.[23] This is especially important for autism communities across the globe, because most existing interventions were developed in European and North American societies and relatively well resourced communities, and then translated, disseminated, and used in other regions. Whether and how locally developed additional or modified interventions can help to ensure best care for autistic people and their families across different contexts globally is an open question.

Finally, in view of the notion that autism and commonly co-occurring conditions (eg, ADHD, epilepsy, intellectual disabilities, anxiety, gastrointestinal conditions, and sleep problems) have shared causes and developmental mechanisms, these conditions should not be studied in isolation as if they were unrelated. A trans-diagnostic approach should be taken for future research into causes and mechanisms, and for intervention and support, to provide evidence that can be readily applied in real-life settings, accounting for naturally complex individual differences.

Contributors
All authors conceived the framework of review, contributed to the writing, and approved the final version of the manuscript. M-CL performed the literature review and drafted the manuscript.

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