Chapter 4: Interventions

Which Interventions Will Improve Health and Well-Being?

Aspirational Goal: Develop a range of interventions that optimize outcomes across the lifespan to maximize the health and well-being of people on the autism spectrum.

Introduction

The evolution of the Aspirational Goal for this chapter reflects the progression of priorities in the autism community. Over the past several years, the IACC's focus has shifted from "preventing disabilities", to encouraging "building adaptive skills", and now emphasizes the construction of lifespan approaches and more meaningful intervention outcomes for individuals on the autism spectrum and their families. This change is driven by the recognition that the goal of autism interventions is not to force autistic individuals to mask their autistic traits, become neurotypical, or lose their identity. Rather, the goal of interventions is to promote positive outcomes for people on the autism spectrum that are meaningful to them. To achieve this goal, researchers, service providers, and policy makers must seek out and include autistic voices and incorporate the diverse lived experiences of individuals on the autism spectrum and their families in the research and implementation of autism interventions so that all individuals across the autism spectrum can achieve their unique goals.

In recent years, research has focused on the development and improvement of interventions that can promote health and well-being for people on the autism spectrum by addressing autism, its co-occurring conditions, or other factors that impact quality of life. Important progress has been made in behavioral and developmental interventions, with a number of interventions leading to improvements in language and social skills development in randomized clinical trials. With increased understanding of the genetic and molecular basis of autism, there have been many clinical trials testing the therapeutic efficacy of molecules and medications to enhance function and manage co-occurring conditions. Interventions to help adults with autism improve their daily living skills and emotional and mental health are also under development. In addition, technological advances have allowed the development of more communication and social training tools for autistic individuals and improved access to interventions for some underserved communities. These are all examples of promising advances in autism intervention with the potential to improve the health and well-being of people on the autism spectrum.

Though progress is being made in several areas for interventions, there is a continuing need for improvements and evidence-based interventions for areas with little coverage, such as interventions for sensory issues and interventions that are effective for individuals with autism who experience challenging behaviors or self-injurious behaviors. Many more intervention options are needed for adults with autism as well. There are many obstacles to be overcome in advancing research on interventions for autism. The heterogeneity (variability from one person to another) of autism creates challenges in planning studies and interpreting results. Interventions may be highly effective for some people and ineffective for others depending on each person's individual combination of characteristics and challenges. This can lead to relatively small sample sizes and potential bias in the reporting of outcomes. More randomized controlled trials with larger samples are needed to determine the efficacy and effectiveness of many interventions. There may also be differences in how interventions work in males versus females with autism or in different cultural settings. Disparities in access to interventions remain for ethnic and racial minority groups and others from underserved communities. Prioritizing

understanding which interventions work and for whom will allow us to develop and personalize new and improved interventions to meet the diverse needs of all individuals across the autism spectrum as they progress through the lifespan.

Behavioral and Developmental Interventions

Behavioral and developmental interventions play a prominent part in the lives of many young children on the autism spectrum. These interventions typically seek to take advantage of the neural plasticity in early development to help autistic children develop strengths and life skills that will promote successful learning and social participation in school, recreational, and home environments. Indeed, recent data shows that pre-emptive interventions before a formal diagnosis may lead to long-term positive outcomes.[1] Many behavioral and developmental interventions for formally diagnosed children on the autism spectrum have been reported to lead to significant improvements in intelligence quotient (IQ), language, and social functioning domains.[2, 3]

However, given the number of different available interventions, it can be overwhelming for families to choose the most effective intervention for their child. Additionally, some methods call for over 20 hours per week of interventions, which may be cost-prohibitive for some families. A recent randomized controlled trial comparing different intervention types and intensities did not find differences in outcomes for young children on the autism spectrum based on intervention style or intensity, but instead the initial autism characteristics observed seemed to be correlated with outcome.[4] A meta-analysis of studies on autism interventions found that most studies were subject to significant bias of various kinds, including detection bias (when assessors are aware of the group assignment of individual participants), reporting bias (selective reporting of only certain outcomes), and performance bias (when participants and/or study personnel are knowledgeable of assigned interventions or groups).[3] These findings highlight the need to compare the effectiveness of different intervention approaches to determine what interventions work best and how, using larger, better designed, and more rigorous randomized controlled trials.

In addition, it is important to recognize that interventions may not be equally effective or necessary for all individuals on the autism spectrum. Given the heterogeneous nature of autism, individuals across the autism spectrum experience diverse challenges, have varied strengths, and may respond differently to and need different interventions. Additionally, the strengths, challenges, and needs of autistic individuals may change over time. Therefore, long-term follow-up of interventions to determine quality of life outcomes and development of interventions for adolescents and adults are important areas of future research. Ultimately, a better understanding of what interventions work best, for whom, when, and how will allow all individuals across the autism spectrum to overcome challenges, fully develop desired skillsets and their strengths, and maximize their health and well-being.[5]

Applied Behavior Analysis

Applied behavior analysis (ABA) is the most commonly practiced behavioral intervention for autism. Current ABA practices include the Early Start Denver Model (ESDM), Picture Exchange Communication Systems (PECS), Discrete Trial Training (DTT), and Pivotal Response Treatment (PRT),[6] and the basic premise for all of these methods is positive reinforcement of desired behaviors to develop necessary skills and reduce behaviors that interfere with health and well-being, such as self-injurious behaviors. Meta-analysis of studies using ABA showed significant improvements in socialization, communication,

and expressive language,[6] though few well-designed randomized controlled trials exist to definitively show the impact of ABA interventions on social and developmental outcomes.[3]

Historically, ABA was developed to teach autistic children to behave in a neurotypical manner. ABA also incorporated rewards for desired behavior and negative reinforcements to discourage undesirable behaviors, such as repetitive or disruptive behaviors. There is now recognition, however, that some of the behaviors that were discouraged are rooted in the needs and sensory experiences of individuals and thus should not be suppressed or stigmatized. In addition, it has been realized that the focus of ABA on encouraging neurotypical behaviors sometimes led to masking of autistic characteristics and led to shame and stress for autistic individuals. This legacy has led to controversy around the use of ABA in the autism community.[7] There are many forms of ABA and the results can vary based on how therapy is delivered as well, resulting in a variety of experiences. Some members of the autism community argue that behavioral differences are part of what makes people on the autism spectrum unique and that the responsibility should be placed on society to understand and accommodate autistic people as they are and celebrate differences. They also object to ABA's focus on eliminating certain behaviors, particularly self-soothing behavior such as hand flapping, without acknowledging the emotional purpose those behaviors serve. Others in the autism community have found ABA to be a very helpful type of therapy that has enabled autistic people to learn skills that have resulted in more success in social and school settings.

ABA has been greatly expanded upon and has evolved since its inception. In comparison to DTT, which was a rigid, clinician-led intervention, current models such as PRT and ESDM allow the children to take the lead and is much more focused on play, developing necessary skills, and reducing self-injurious and aggressive behaviors. To alleviate concerns in the community, larger randomized controlled trials and longitudinal studies should be conducted to definitively demonstrate the potential immediate and long-term benefits and harms of ABA interventions, and efforts need to be made to prevent any possible negative effects of ABA. The goals of ABA should also be decided by the person receiving the intervention or, if they are unable to communicate their desires, their caregivers and guardians with the goals of the autistic individual in mind. Researchers and clinicians should also recognize that ABA simply may not be suited for some individuals on the autism spectrum, and, in such cases, they should be pointed to other forms of interventions to meet their goals and maximize their positive outcomes.

Naturalistic Developmental Behavioral Interventions

Naturalistic Developmental Behavioral Interventions (NDBIs) are based on ABA principles but use a strengths-based model to teach skills in a developmental sequence and in a naturalistic environment, such as during play or other daily activities, with natural rewards (for example, when the child says "car", being rewarded with a toy car as opposed to a piece of candy).[8] Examples of NBDIs include ESDM, PRT, and Joint Attention Symbolic Play Engagement and Regulation (JASPER). These approaches emphasize the integration of knowledge and skills across developmental domains and are taught in a social context that is emotionally meaningful to the individual. Meta-analysis of autism intervention literature showed that NDBIs are the most well supported by randomized controlled trials, indicating it is effective in supporting development of social communication, language, and play skills.[3, 9]

Despite data supporting the effectiveness of NDBIs, a recent survey of behavior professionals indicated that most had no knowledge of NDBIs and few believed them to be appropriate or effective.[10] Therefore, more training and outreach to service providers are needed to implement NDBIs more

widely. In addition, it is unclear what components of NDBIs are necessary for improvements in social communication, language, and play skills development. Additional randomized controlled trials on a larger scale are needed to determine what the key components of NDBIs are for success. Future research should also address what the long-term gains are following NDBI and how to improve NDBIs to facilitate the development of skills and strengths across the lifespan.

Interventions in the Classroom

School-aged children spend much of their day in the classroom, and autistic children may struggle with sensory, social, and cognitive issues that make learning difficult. Thus, researchers are increasingly developing and testing interventions in school-based settings, from preschool through high school.[11, 12] Studies indicate that these interventions are effective at increasing classroom engagement,[13] improving socialization,[14] and reducing disruptive behavior.[15] As a whole, these and other findings highlight the effectiveness of teacher-implemented interventions in school settings to improve the educational experience for children on the autism spectrum and pave the way for more and continued school-based intervention research. Future research should explore how to best balance academic programming with special education interventions to develop needed life skills and improve social communication and transition preparedness. Additionally, schools should provide resources so that teachers and other school personnel have the training and support necessary to successfully implement interventions in the classroom. Disparities in funding and resources for autism interventions in schools, particularly in underserved communities, must also be addressed.

Family-Mediated Interventions

As diagnostic advances have made it possible to identify children on the autism spectrum at earlier ages, researchers have tested a number of parent- and sibling-mediated interventions in order to meet the need for interventions that can be implemented as early as possible in the home setting. Studies show that family-mediated interventions can facilitate social, cognitive, and language development in children on the autism spectrum,[16-19] and the presence of a sibling greatly increases the development of adaptive skills.[20] Additionally, active hands-on parent coaching is more effective than parent education models where the same information is provided without active coaching.[16] Caregiver-mediated intervention can also be cost-effective and reinforcing of family support.

Continued research is needed on how to best train parents and caregivers to provide effective and efficient interventions for their child, recognizing that parents and caregivers may already be overburdened and may only have limited resources to devote to training and implementation. Family-mediated interventions can serve as an early start to intervention at home and continue as an adjunct to other types of interventions that may be delivered in school settings or with a professional. Ideally, training for parents should evolve over time as the needs, abilities, and strengths of their child changes. Future research should also explore how training involving the whole family, including siblings, may be helpful in further facilitating the development of children on the autism spectrum. Caregiver skills training has been developed for some specific populations, including the Autism Speaks and Color of Autism's partnership on the World Health Organization Caregiver Skills Training Program that provides caregiver skills training support in international and U.S. communities, with a focus on low-resource settings. However, more work is needed to develop culturally and linguistically appropriate interventions for all caregivers of individuals on the autism spectrum.

Peer-Mediated Interventions

Peer-mediated interventions can also help maximize positive outcomes for individuals on the autism spectrum and can result more inclusive environments for individuals on the autism spectrum. These types of interventions typically pair autistic individuals with neurotypical individuals to improve social interactions, and studies have shown that peer-mediated interventions can improve social skills in both children and adults on the autism spectrum.[21-25] Interventions mediated by autistic peers have also been shown to be effective[26] and may be especially valuable as individuals on the autism spectrum can bring their own lived experiences to better personalize the intervention. More research is needed on the long-term impact of peer-mediated programs and to determine who would most benefit from peer-mediated interventions. Additionally, peer-mediated interventions are mostly limited to school settings, though programs such as Pennsylvania's Community Autism Peer Specialist (CAPS) Training to train autistic peers in delivering peer support services are becoming available in community settings. Studies are needed on how to best implement peer-mediated interventions in different settings, and the efficacy of these programs, both immediate and in the long term, need to be determined.

Technology-Based Interventions and Communication Tools

Digital-based technological interventions for individuals on the autism spectrum have continued to increase in accessibility, breadth, and depth of use. Scientific evidence for the effectiveness of technology-based or technology-enhanced interventions has increased, with a large number of randomized controlled trials highlighting the breadth of technological applications in autism research as well as their increasing rigor. Technology-based interventions have tremendous potential to benefit individuals on the autism spectrum in many ways, including by helping them improve social and communication skills and gain greater independence, all of which can help individuals on the autism spectrum achieve their goals and promote positive outcomes.

Telehealth, which uses technologies such as videoconferencing to allow specialists and care providers to deliver interventions remotely, has becoming increasingly popular in recent years.[27-29] Within the autism community, telehealth programs typically rely on specialists to provide training and supervision to teachers, clinicians, and caregivers of children on the autism spectrum. This remote training has proven to be effective and led to significant improvements in child outcomes.[27] Telehealth is a promising and cost-effective way of delivering needed interventions to a broader swath of the autism community, particularly those living in rural areas for whom specialists may not be within easy reach. However, more large-scale randomized controlled trials are needed to better understand the effectiveness of telehealth interventions. Additionally, most studies on telehealth are focused on children and improving communication skills and decreasing challenging behavior. Future studies should expand to include autistic individuals of all ages and explore other areas of intervention such as social skills (e.g., joint attention) and for co-occurring conditions.

Extended reality (XR) technology, encompassing both virtual and augmented reality, gives users an immersive and interactive environment. Rapid advancements in XR technology over the past few years have led to its increased use in leisure gaming and education. The use of XR technology has also been explored in providing interventions to individuals on the autism spectrum to improve social communication skills, emotion regulation and control, and daily living skills, with positive results so far.[29-31] Additionally, XR interventions are typically well-tolerated and accepted by both autistic individuals and their caregivers.[29] However, improvements still can be made. The scenarios typically

used in XR interventions tend to be limited in both number and scope and very confined, making it difficult to develop skills needed to adapt to changes. Additionally, because the virtual environment is not the real world, it is difficult to generalize behaviors in XR to the real-world settings. More research is needed on how perceived reality impacts the efficacy of XR interventions and how to overcome those challenges. Larger studies with more diverse participants are also needed to determine if the results so far are reproducible and relevant across the autism spectrum and in diverse racial and ethnic groups. The safety of XR technology and extended use of XR technology must also be carefully studied.

Robot-assisted technology and artificial intelligence (AI) have been tested in recent years to assist individuals on the autism spectrum with developing learning and social skills.[32-38] Most studies using robots and artificial intelligence report positive improvements and outcomes following intervention and therapy, showing that this is a promising area of future research. Additional trials are needed to determine the reproducibility and generalizability of these results, and future studies should consider long-term follow-up to determine how long improvements last. Considerations should also be given to intervention areas beyond learning and social skills development and how to tailor robots to the specific needs of each autistic individual.

Given the ubiquity of smart phones and personal tablets, mobile applications (apps) are increasingly popular and accessible and are being used for a variety of autism interventions, including speech therapy, improving communication, and building social skills.[39-43] Studies on the use of apps to facilitate skills building have reported improvements in communication and social interactions, and participants typically report greater interest and motivation to participate in the intervention. App developers should use training materials that reflect real-world situations so that learned skills are translatable and implement programming is adjustable with improvements in skill development. Future studies should also explore how AI can be used to in apps to monitor body language and performance to objectively track improvements in social, communication, learning, and other skills.

Many individuals on the autism spectrum have difficulties with spoken and verbal communication. Augmentative and alternative communication (AAC) tools are increasingly adapted to allow both speaking and nonspeaking individuals to communicate with others more effectively. Assisted modalities of AAC including PECS and speech generating devices (SGDs) have been particularly useful,[44] especially for functional communication such as making requests.[45] More research is needed on how to use AAC and other interventions to facilitate communication of more complex ideas. Additionally, AAC use has traditionally been prescribed only after other interventions to induce verbal speech has failed. However, evidence suggests that AAC use may in fact facilitate improvements in spoken communication.[46] Therefore, research is needed on when the introduction of AAC can be most impactful in promoting both spoken and unspoken communication. It will be important to study how AAC use may benefit older adolescents and adults on the autism spectrum who may not have had previous access to tools for effective communication. Efforts also need to be made to remove barriers to AAC use, including ensuring that AAC use is normalized[47] and validated in educational and health care settings so all individuals on the autism spectrum can communicate effectively.

Wearable technologies such as smart watches have become more commonplace and are now being tested for a variety of uses for individuals on the autism spectrum. So far, wearable technology has mostly been used to gather information on different physiological processes.[48, 49] This information can be useful in predicting episodes of aggression or increased stress and anxiety.[50-55] Wearable technology

has also been used to facilitate effective communication and improve socialization by detecting facial expressions, allowing mentors to provide virtual prompts in social situations, and learning and interpreting gestures made by autistic children.[56-58] In addition, wearable sensors can be used to monitor co-occurring conditions such as epilepsy to facilitate timely care.[59, 60] Research on how wearable technology can be used in interventions for autism and co-occurring conditions is just beginning. The preliminary results so far need to be validated in larger randomized controlled trials, and more research is necessary on the long-term efficacy and safety of using wearable technology.

Technology-based interventions and tools have become increasingly effective, important, and useful. Yet a number of challenges and gaps have been highlighted above. Several concerns are also shared across many of these technologies. For example, with cloud data storage and transfer becoming more common, data privacy and confidentiality issues will need to be addressed when using and developing technology-based tools. Additionally, many of these technologies, including robot-assisted technology and AAC, require training for caregivers, teachers, and clinicians for effective use. More efforts are needed to ensure that such training is available and accessible and that tools are developed with usability in mind. Importantly, some families may not have access to basic resources such as stable high-speed internet to take advantage of these interventions and tools. Efforts need to be made to improve access to technology-based interventions for everyone in the autism community, particularly for those in underserved communities.

Medical and Pharmacological Interventions

Pharmacological Interventions

Only two medications, risperidone and aripiprazole, currently have Food and Drug Administration (FDA) indication for use in autism, specifically to address irritability, and both of these drugs are associated with side effects such as weight gain and drowsiness that may not be desirable.[61-63] There are no approved pharmacological interventions that address other core features of autism such as social communication difficulties.

Advances in genetics and neurobiology have led to an increase in the number of clinical trials testing medical interventions for autism.[64, 65] However, no new drugs so far have succeeded in clinical trials since the *2016-2017 IACC Strategic Plan* was published. For example, the neuropeptides oxytocin and vasopressin are known to be involved in social cognition and have been investigated in a number of autism studies.[66] Multiple clinical trials have now been conducted with intranasal oxytocin, but the results do not indicate a significant improvement in social functioning compared to placebo.[67-71] Large clinical trials for balovaptan, a vasopressin V1a receptor antagonist, also did not show significant results compared to placebo controls.[72-75]

Several major challenges exist when conducting clinical trials for autism. Given the range and variability of challenges people on the autism spectrum may face, additional research efforts must be directed to increase study sizes and group individuals with similar traits and challenges together. This will increase help researchers determine if there may be specific subsets of autistic individuals for whom certain interventions may work. In addition, current outcome measures for changes in social functioning that are used to judge whether an intervention worked or not rely on self or caregiver report. Such self-reported measures may be highly subject to bias and the placebo effect, where trial participants may report feeling better than what is indicated when the intervention effect is measured through an

objective method, such as a blood test or laboratory measurement. Biomarkers and more objective and sensitive reporting tools need to be developed to collect more accurate data.

Efforts should also be made to determine how genetic factors may influence the response to different medications, paving the way for precision medicine and personalized pharmacological interventions in autism. In particular, advances in the study and treatment of Rett syndrome, Fragile X syndrome (FXS), and tuberous sclerosis complex have laid the groundwork for similar mechanism-based treatment trials in genetic disorders associated with autism. For example, a recently completed phase 2 clinical trial demonstrated cognitive benefits associated with an inhibitor of PDE4D, a protein important for learning and memory, in individuals with FXS.[76] However, translating success from animal studies has not always been straightforward to date, and intellectual disability commonly found in individuals with these neurogenetic disorders can pose ethical and logistical obstacles in designing studies in this field.

In fact, many of the drug trials in autism exclude individuals with intellectual disability and very young children due to ethical and/or practical challenges. However, a mechanism-based intervention intended to improve social and communication challenges associated with autism may be more effective if administered relatively early in life and may be most effective in those with higher support needs. Thus, it is crucial that such individuals are included in upcoming trials. This will require researchers to carefully consider how interventions can be adapted to accommodate individuals across the entirety of the autism spectrum and of all ages and identify age- and ability-appropriate outcomes and outcome measures.

Noninvasive Brain Stimulation

Noninvasive brain stimulation (NIBS) methods, specifically transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are additional experimental methods being tested for their potential to identify neural mechanisms and enhance brain function in autism.[77] TMS can potentially offer a non-invasive tool to study aspects of brain differences in autism and intervene in aspects of autism such a repetitive behaviors and executive function by modulating brain plasticity and network activity. In particular, repetitive TMS (rTMS) can alter brain excitability and network activity beyond the duration of a stimulation session and is being examined as an intervention that could potentially improve social skills, as well as communication, cognitive, and learning skills. tDCS induces neuronal plasticity (changes in brain cells) by altering membrane potential (electrical charge), and its effects can also last beyond the intervention session, depending on the duration and intensity of the stimulation.

Recent reviews of studies using NIBS indicate improvements in restricted, repetitive behavior and executive functioning, as well as changes in the objective measure of brain wave patterns.[78-80] However, the clinical applications of these methods still cannot be determined as many studies were open-label trials, where participants knew which intervention they were receiving. Additionally, the controlled trials used neurotypical individuals as opposed to faux stimulation as a control. Therefore, better study designs are needed to determine the true effectiveness of TMS and tDCS as an intervention for autism. Additionally, NIBS trials must expand the pool of study participants to include individuals of all ages across the autism spectrum, and longitudinal studies need to determine what the long-term outcomes are following brain stimulation. Data on safety and side effects also need to be carefully assessed and reported. Though preliminary results indicate that NIBS is safe,[81] very few studies include detailed data

on experienced side effects. These are important considerations for future studies to improve the tolerability and feasibility of NIBS interventions.

Stem Cell Therapy

Stem cell technology is advancing our understanding of typical and atypical neurobiological processes, thereby offering potential new opportunities for treating neurodevelopmental disorders and co-occurring conditions, including in autism. Some studies suggest that the pathophysiology of autism may involve immune dysregulation and neuroinflammation.[82] Stem cell therapies are thought to modulate immune system activity and facilitate neural connectivity and are being tested as interventions for autism, with the goal of improving issues such as social communication.[83, 84] Stem cells used in trials are derived from sources such as bone marrow and cord blood. While some small studies conducted so far have reported positive results,[83-86] there have also been ethical concerns about this area of research related to financial conflicts of interest among those conducting studies and inadequate ethics review of the study protocols.[87, 88] Though there are companies already marketing stem cell therapies, this research is only just beginning, and there are many hurdles to overcome and unanswered questions to address before the field will know whether stem cell therapy can be a safe and effective intervention for autism. Future studies will need to use standardized and validated outcome measures with large samples to ensure that results are unambiguous and reproducible. Additionally, more research is needed to determine the proper dosage and cell source to be used in stem cell therapies and if they are effective. This will be an important area of investigation to monitor as researchers work to answer these questions and replicate and expand initial findings.

Complementary and Alternative Approaches

Complementary and alternative interventions have also been used by some in the autism community. These include mindfulness, art therapy, animal-assisted interventions, yoga, and interventions such as special diets (e.g., gluten-free, casein-free) and supplements, probiotics, and plant-based and herbal medicines. While many people may be using complementary and alternative approaches, the evidence base for these interventions is not yet established. Further research is needed to establish the efficacy of these approaches and whether they should be included more routinely in wellness strategies for individuals with autism.

Studies of the effect of special diets and supplements on social skills and restricted, repetitive behavior have had mixed results, and data so far is not strong enough to support the recommendation of such interventions for individuals on the autism spectrum.[89-92] The number of studies on this topic suggests there is great interest in further understanding how nutritional status may relate to autism presentation. Future studies should be more rigorously designed and include more participants with longer follow-up periods to provide conclusive evidence as to the efficacy of special diets and supplements in improving quality of life for people on the autism spectrum.

Results for the effect of probiotics are similarly mixed, with randomized controlled trials showing no effect on autism symptom severity, though studies with prebiotic supplementation seem to produce more consistent results.[93, 94] More rigorous and better designed randomized controlled trials with larger and more diverse samples are needed to provide insight into how probiotics and prebiotics may improve autism symptoms. Additionally, while these interventions are generally considered safe in the short-term, the long-term effects of these interventions are not known, and future studies should be conducted on the safety of these interventions and any potential long-term side effects.

The number and severity of side effects associated with commonly prescribed pharmaceuticals have led to increased interest in plant-based medicines and herbal remedies as interventions for both core traits of autism and co-occurring physical and mental health conditions. Plant-based compounds such as cannabinoids, resveratrol, curcumin, and those found in green tea extract show potential therapeutic effects for autism in preliminary studies.[95, 96] However, the exact benefits and side effects of these compounds still need to be established using carefully designed large clinical trials.

Approaches such as mindfulness, art therapy, animal-assisted interventions, and yoga have been used to improve emotional regulation, enhance social relationships, and reduce aggression and irritability.[97-103] Results of studies so far seem to indicate that art and music therapy may be useful in promoting nonverbal expression and improving communication,[98, 103] and dance therapy may improve social functioning and intimate relationships between adults.[99, 104] Some studies indicate that equine-assisted interventions and horseback riding may also improve social communication and behavioral skills.[97, 105, 106] However, limited effects have been found for other animal-assisted therapies and mindfulness-based approaches.[97, 101, 102] Studies on these alternative interventions tend to be small with a limited number of participants followed for a short window of time. Larger, better powered, more rigorous studies are needed to determine what short- and long-term benefits these alternative approaches may have for individuals on the autism spectrum.

Lastly, sensory hyperreactivity and hyporeactivity are common in individuals on the autism spectrum and can impact health and well-being.[107-110] However, very few sensory-based interventions have been studied for individuals on the autism spectrum, and the available interventions (such as Sensory Integration Therapy, massage, and the use of weighted blankets) show little evidence to support their effectiveness [3]. Much more research is needed to develop appropriate and effective interventions to improve sensory outcomes for individuals on the autism spectrum.

Interventions for Co-occurring Conditions

A number of intervention trials target co-occurring mental health conditions in autism. This is a particularly important area of research as the presence of a co-occurring mental health condition is predictive of lower quality of life for autistic individuals.[111] Pharmacological interventions for co-occurring conditions in autistic individuals typically involve prescription of drugs tested and approved for the co-occurring condition alone.[112] For example, children on the autism spectrum with co-occurring epilepsy are treated with anti-epileptic drugs such as valproic acid,[112] and autistic children with ADHD are given stimulants such as methylphenidate.[113] However, these drugs have been associated with significant side effects in individuals on the autism spectrum, who may be more sensitive to adverse reactions. Therefore, careful analyses need to be conducted to determine whether medications prescribed for co-occurring conditions are safe in autistic individuals, and additional pharmacological alternatives are needed so that individuals on the autism spectrum can treat co-occurring conditions effectively with minimal side effects.

In addition to pharmacological interventions, psycho-social interventions may also be effective for some co-occurring conditions. For example, cognitive behavior therapy (CBT) has been shown to be an effective treatment for anxiety, including for children and adults on the autism spectrum.[114-117] However, anxiety and other mental health conditions may present differently in autistic versus neurotypical individuals. More research is needed to better identify symptoms of anxiety and depression in individuals on the autism spectrum, and interventions tailored for autistic individuals may be more

helpful than just standard treatments. In addition, efforts so far have been mostly focused on speaking autistic children without intellectual disabilities,[118, 119] limiting the applicability and generalizability of findings. Future studies should include study participants from across the entirety of the autism spectrum and of all ages, as well as female participants and people from underrepresented racial and ethnic groups.

Multiple studies have shown the efficacy of behavioral therapies and melatonin in treating sleep problems in children on the autism spectrum,[120, 121] and pediatric-appropriate prolonged-release melatonin has been found to be safe and well tolerated with minimal side effects.[122, 123] Other interventions such as the use of weighted blankets, aromatherapy, exercise, and yoga to improve sleep have more limited evidence. Despite the availability of these intervention options, some autistic children still experience sleep difficulties, and many autistic adults report dissatisfaction with their sleep quality.[124] More research is needed to determine if existing medication for primary insomnia improves sleep for autistic people for whom non-pharmacological interventions are not effective and what the side effects may be. Additionally, studies are needed to determine how best to deliver training to parents in the use of behavioral strategies to improve their child's sleep quality. Studies to develop sleep interventions for adults on the autism spectrum are also greatly needed to improve health and well-being throughout the lifespan.

Weighted blankets, aromatherapy, exercise, mindfulness, massage yoga, dance, and animal/pet therapy are all methods that some families and autistic people seek out to help with stress, anxiety, emotional regulation, and sensory awareness. While these modalities may not be clinically-proven to be effective for addressing the aforementioned conditions in the context of autism specifically, they are complementary approaches that can be used by individuals to meet their personal needs or be used alongside mainstream, evidence based approaches to enhance well-being.

For co-occurring gastrointestinal (GI) problems, treatment generally involve changes to the gut microbiota.[125] Fecal microbiota transplantation (FMT) is an emerging intervention that some are using to try to address a range of concerns, from behavioral concerns, mental health issues, and dietary issues.[126, 127] However, larger randomized controlled trials with diverse study participants are still needed to demonstrate the efficacy and safety of FMT. In addition, research should focus on developing effective alternative approaches to treat GI problems in individuals on the autism spectrum. In particular, food aversions and limited diets may play a role in exacerbating GI issues, and behavioral approaches may be effective in promoting a healthier and more diverse diet and improving quality of life. Dietary and nutritional interventions are also commonly used by parents of children on the autism spectrum as a way to improve both social difficulties associated with autism and to relieve GI symptoms. However, as previously stated, the efficacy of such interventions is not well established.[128] Future research is needed to conclusively determine whether special diets and supplements are safe and effective for treating co-occurring GI discomfort and improving quality of life.

Outcome Measures and Biomarkers

Over the past few decades, significant progress has been made in the development of new behavioral interventions and identification of novel drug targets aimed at reducing disabilities associated with autism and improving quality of life across the lifespan. A major challenge in determining whether new treatment approaches are efficacious has been the measurement of treatment response, which are currently mostly reliant on clinician and caregiver reports. In addition, measurement of treatment

response is particularly complex in autism due to the heterogeneity resulting from an individual's symptom profile, sex, cognitive and language abilities, and developmental level. Moreover, many existing assessment measures were developed for screening and diagnosis and are not sensitive toward assessing changes in symptoms over time.

Considerable effort has been directed toward evaluating which existing measures are suitable for clinical trials and for developing quantitative, objective, and sensitive measures of intervention response. Increasingly, the input of key stakeholders, including autistic individuals and caregivers, is solicited to ensure that outcome measures reflect the priorities and needs of persons for which the interventions are being developed. Biomarkers of intervention success are needed, as are "stratification" biomarkers for matching people to the best intervention for them at the best time. Until it becomes possible to biologically measure intervention response, negative results from pharmacological and behavioral interventions will be difficult to interpret, and positive results may not definitively indicate the requisite dose or duration of treatment. Predictive biomarkers that help to match individuals to particular interventions will help to create more precise treatments and allow individuals on the autism spectrum and their families to avoid wasted time and resources.

Initial efforts have focused on developing measures that are linked indirectly or directly to underlying neural circuitry, which can offer insight regarding whether the intervention is influencing certain aspects of neural circuitry, inform researchers of the mechanisms that may underlie the intervention effects, and predict intervention response. These measures include eye tracking,[129] electrophysiological responses,[130, 131] and magnetic resonance imaging,[132] among others. Such measures can also serve as an early efficacy signal that can detect response to treatment before changes in more distal measures such as language and social abilities are evident. Early efficacy markers can be used to identify which individuals are most likely to benefit from a given intervention and/or in adaptive study designs to indicate early in the trial whether modifications in the intervention (e.g., timing and intensity) should be made.

Given the high risk of failure for central nervous system intervention studies, there is a need to design early-stage trials to incorporate objective measures that adequately test the proposed mechanism of action of the intervention and determine if the intervention target has been modulated. There is also a need for studies that demonstrate the effect of the intervention on the proposed mechanism of target engagement or site of action (e.g., the molecular, circuit, neural or system-based target) prior to an examination of clinical efficacy (an association with behavioral or clinical benefit). Clinical studies for these intervention targets should be designed so that even negative results will provide meaningful information.

Recently, a number of substantial investments have been made to support large, collaborative efforts aimed at validating biomarkers and outcome measures for use in autism clinical trials. These consortia involve public-private partnerships among academia, advocacy and other non-profit organizations, government, and industry, with a goal of reducing risk of investments into pharmacological autism trials and optimizing the success of such trials. These projects are examining a wide range of potential biomarkers and their relationships with observational and caregiver-report measures of behavior in large samples of autistic versus neurotypical individuals over time. Furthermore, regular communication, data sharing agreements, and shared measures across the existing consortia will increase the scientific utility of these investments. One example is the Autism Biomarkers Consortium

for Clinical Trials (ABC-CT), a National Institutes of Health (NIH)-, Foundation for the NIH-, and Simons Foundation-funded consortium of sites that aims to develop, validate, and disseminate objective measures of social function and communication for autism, with the ultimate goal of advancing these measures as markers and predictors of treatment response.[133]

In sum, multiple laboratories are conducting studies to develop better ways of measuring intervention response. Continued investment in such studies will ensure that, as new behavioral and medical interventions are developed, we will have the capability of testing their efficacy. Such investments will also be essential for developing improved methods for identifying specific populations within the autism community that are responsive to specific interventions and identifying the neural mechanisms underlying intervention response.

Research Policy Issues

There has been continued progress in the development and evaluation of multiple intervention types in recent years. There are now tremendous opportunities for combining therapeutic modalities in ways that potentially result in synergistic impacts that are greater than the sum of the parts. More studies on combination therapy approaches may be helpful in determining which therapies may work well in combination for which individuals. One example would be the combination of medications and behavioral interventions or using technology to facilitate improvements in interventions in the classroom. Advancement of new or reconceptualization of existing interventions into therapies organized into therapeutic modules that can be combined and reused in flexible arrangements can potentially offer opportunities for personalizing and finetuning interventions to the needs of the individual. combination therapies may especially be helpful in addressing co-occurring conditions such as anxiety, aggression, and depression. The recent Lancet Commission on the future of care and clinical research in autism laid out a stepped care approach that can be personalized to meet the needs of autistic individuals and their families as their strengths and needs evolve over time.[5] Implementation of a stepped care approach can help promote efficient and equitable distribution of intervention resources, enabling individuals across the autism spectrum to meet their personalized and diverse goals.

Encouragingly, the diversity of study participants in autism intervention research has improved, as researchers more often strive to include underserved communities as well as populations previously excluded or overlooked. However, while representation has increased, participants from racial and ethnic minority groups are still underrepresented overall in autism intervention research,[2, 134] and disparities remain in access to services and interventions.[135, 136] This represents a critical gap in our understanding of how existing interventions may or may not be culturally and linguistically relevant and feasible for autistic individuals from underserved communities. Efforts should be made to include individuals from racial and ethnic minority groups and other underserved communities in intervention research, and culturally and linguistically relevant interventions need to be developed and be widely available so that all autistic individuals can access effective interventions.

Adolescents and adults are another underserved population in autism intervention research as most intervention studies are still focused on young children. Future research should seek to fill this gap by developing effective interventions for autistic individuals across the lifespan. Given the increased understanding that girls and women on the autism spectrum may have a different presentation of autism and face different health challenges compared to autistic boys and men,[111, 137-139] more also

needs to be done to include girls and women on the autism spectrum in intervention research to provide access to effective and sex- and gender-appropriate interventions and outcome measures.

Additionally, there is some evidence to suggest that autistic individuals with higher support needs, including individuals with intellectual disability and those who are minimally speaking or non-speaking, are disproportionately excluded from intervention studies.[5, 140, 141] The challenges of working with this population in research settings may have created barriers, but solutions are needed to ensure that these individuals are represented in research generally and that studies that target their specific set of needs for high-quality interventions and supports are addressed. Accommodations may also need to be made to make it easier for family caregivers to participate. Inclusion of individuals of all levels of ability and support needs across the autism spectrum in research is an important goal to ensure that all autistic people have access to effective interventions, regardless of the level of support needs.

In addition to increasing the diversity of study participants, more research efforts are needed in the area of intervention implementation. A recent systematic review found that clinical guidelines for autism contained recommendations based mostly on expert opinion as opposed to empirical evidence.[142] This highlights the continued need to improve translation of research findings and implementation of evidence-based interventions in autism communities. Importantly, individuals with perceived "low" support needs may still have challenges in daily living, unmet support needs and co-occurring physical or mental health conditions – particularly those conditions and issues that might be "invisible" to others. Issues such as challenges with executive function and mental health concerns such as anxiety, depression, and emotional regulation often can result in significant challenges for autistic individuals even if they live independently or have many other strengths. More research on the connections between unmet needs and social determinants of health on mental health in individuals with autism are needed. Therefore, access to interventions should not be based solely on subjective observations of an individual in clinical situations; rather, interventions should be available to those who report and demonstrate their need for support, regardless of their perceived cognitive and linguistic abilities.

Future resources should be directed towards increasing the accessibility of evidence-based interventions by improving community access to information about the efficacy and safety of different interventions (including rapid dissemination of novel interventions), improving and strengthening the autism service providers workforce, providing resources to navigate insurance and Medicaid/Medicare systems, and reducing disparities in intervention access and resources. By focusing on practical barriers to ultimate intervention deployment, including insurance, provider adoption willingness, and marginal expenses, a more robust, efficient, and complete pipeline from idea to effective individual treatment can be realized.

Summary

While there have been multiple, important advances in the field of autism interventions, there is still much progress to be made. Researchers must continue to develop new interventions as well as improve on existing interventions for diverse settings and populations, including males and females, individuals with co-occurring conditions and varying levels of support needs, individuals across the lifespan, and those in settings or communities that are under-resourced or underserved. Efforts must also be made to improve community implementation of evidence-based interventions and improve community access to interventions proven to be effective to maximize positive outcomes for individuals on the autism spectrum. Importantly, the voices of autistic people, their families, and potential providers must be

included in intervention research and implementation in a participatory and community-based approach. This will maximize the utility and relevance of the research.[5] Furthermore, autistic individuals and their caregivers must be allowed to choose what interventions work best for their unique needs to meet the diverse goals of individuals across the autism spectrum.

Recommendations

RECOMMENDATION 1: Develop and improve pharmacological and other medical interventions that will maximize positive outcomes for individuals on the autism spectrum.

Examples:

- Advance the study and treatment of genetic syndromes related to autism (including, but not limited to, RTT, FXS, and TSC) and utilize the groundwork provided by investigations of these disorders to develop similar mechanism-based, genetically targeted pharmacology treatment trials for autism.
- Explore innovate intervention modalities and combination therapies.
- Development interventions to address challenges across the autism spectrum and across the lifespan
- Investigate intervention response, including how girls and women on the autism spectrum respond differently to intervention approaches.
- Determine the safety and efficacy of pharmacological interventions for common co-occurring conditions such as mental health conditions, ADHD, gastrointestinal disorders, and sleep disorders in autistic populations.
- Develop biomarkers that can help inform decisions about the most appropriate interventions for particular individuals across the autism spectrum and provide objective, early assessments of response to intervention.

RECOMMENDATION 2: Create and improve a variety of psychosocial, developmental, occupational, and educational interventions that will maximize positive outcomes for individuals on the autism spectrum.

Examples:

- Support research to ensure that interventions are developed that can address various subsets of individuals as well as the whole autism spectrum, the whole lifespan, and diverse populations (including girls and women, minimally speaking individuals, intellectually disabled individuals, adults, and individuals in under-resourced and underserved communities) and that interventions are accessible across settings, communities, and income levels.
- Develop interventions that can address the needs of autistic people across the whole lifespan – early childhood, adolescence, early adulthood, middle age, and older adulthood – that offer a path toward continued learning and development of life skills, and that maximize positive outcomes.
- Identify the characteristics and components of, and contributors to, successful therapeutic approaches as a basis for future innovation and tailoring of interventions to particular populations or settings.
- Explore combination therapies.

- Develop outcome measures that include biomarkers of treatment success, measures of improvement across multiple domains, and improvements in health and well-being.

RECOMMENDATION 3: Develop and improve technology-based interventions that will maximize positive outcomes for individuals on the autism spectrum.

Examples:

- Develop technology-based interventions that help people on the autism spectrum improve their social and communication skills, increase their independence, and in many other ways help improve the quality of their lives.
- Develop tools allowing individuals on the autism spectrum to track and direct their own interventions.
- Development interventions for minimally speaking individuals and those with intellectual disabilities, with a focus on the use of technology to augment communication as well as adaptive, individualized intervention approaches for both of these underserved groups.
- Increase access to interventions by developing technology-based interventions that can be deployed outside of primary care or clinical settings.

References

1. Whitehouse, A.J.O., et al., *Effect of Preemptive Intervention on Developmental Outcomes Among Infants Showing Early Signs of Autism: A Randomized Clinical Trial of Outcomes to Diagnosis.* JAMA Pediatrics, 2021. **175**(11): p. e213298.
2. Hume, K., et al., *Evidence-Based Practices for Children, Youth, and Young Adults with Autism: Third Generation Review.* Journal of autism and developmental disorders, 2021. **51**(11): p. 4013-4032.
3. Sandbank, M., et al., *Project AIM: Autism intervention meta-analysis for studies of young children.* Psychological bulletin, 2020. **146**(1): p. 1-29.
4. Rogers, S.J., et al., *A Multisite Randomized Controlled Trial Comparing the Effects of Intervention Intensity and Intervention Style on Outcomes for Young Children With Autism.* Journal of the American Academy of Child and Adolescent Psychiatry, 2021. **60**(6): p. 710-722.
5. Lord, C., et al., *The Lancet Commission on the future of care and clinical research in autism.* The Lancet, 2022. **399**(10321): p. 271-334.
6. Yu, Q., et al., *Efficacy of Interventions Based on Applied Behavior Analysis for Autism Spectrum Disorder: A Meta-Analysis.* Psychiatry investigation, 2020. **17**(5): p. 432-443.
7. Leaf, J.B., et al., *Concerns About ABA-Based Intervention: An Evaluation and Recommendations.* Journal of autism and developmental disorders, 2022. **52**(6): p. 2838-2853.
8. Schreibman, L., et al., *Naturalistic Developmental Behavioral Interventions: Empirically Validated Treatments for Autism Spectrum Disorder.* Journal of autism and developmental disorders, 2015. **45**(8): p. 2411-2428.
9. Crank, J.E., et al., *Understanding the Effects of Naturalistic Developmental Behavioral Interventions: A Project AIM Meta-analysis.* Autism research : official journal of the International Society for Autism Research, 2021. **14**(4): p. 817-834.
10. Hampton, L.H. and M.P. Sandbank, *Keeping up with the evidence base: Survey of behavior professionals about Naturalistic Developmental Behavioral Interventions.* Autism, 2021. **26**(4): p. 875-888.
11. Hugh, M.L., et al., *School-Implemented Interventions for Preschool to High School Students with Autism: An Update on Recent Research.* Current Psychiatry Reports, 2021. **23**(9): p. 54.
12. Odom, S.L., et al., *Educational Interventions for Children and Youth with Autism: A 40-Year Perspective.* Journal of autism and developmental disorders, 2021. **51**(12): p. 4354-4369.
13. Boyd, B.A., et al., *Efficacy of the ASAP Intervention for Preschoolers with ASD: A Cluster Randomized Controlled Trial.* Journal of Autism and Developmental Disorders, 2018. **48**(9): p. 3144-3162.
14. Vivanti, G., et al., *Outcomes of children receiving Group-Early Start Denver Model in an inclusive versus autism-specific setting: A pilot randomized controlled trial.* Autism, 2018. **23**(5): p. 1165-1175.
15. Beqiraj, L., et al., *Positive behavioural support for children and young people with developmental disabilities in special education settings: A systematic review.* Journal of Applied Research in Intellectual Disabilities, 2022. **35**(3): p. 719-735.
16. Landa, R.J., *Efficacy of early interventions for infants and young children with, and at risk for, autism spectrum disorders.* International review of psychiatry (Abingdon, England), 2018. **30**(1): p. 25-39.
17. Pacia, C., et al., *A Systematic Review of Family-Mediated Social Communication Interventions for Young Children with Autism.* Rev J Autism Dev Disord, 2022. **9**(2): p. 208-234.

18. Rojas-Torres, L.P., Y. Alonso-Esteban, and F. Alcantud-Marín, *Early Intervention with Parents of Children with Autism Spectrum Disorders: A Review of Programs.* Children (Basel, Switzerland), 2020. **7**(12): p. 294.
19. Swanson, M.R., *The role of caregiver speech in supporting language development in infants and toddlers with autism spectrum disorder.* Development and psychopathology, 2020. **32**(4): p. 1230-1239.
20. Rosen, N.E., J.B. McCauley, and C. Lord, *Influence of siblings on adaptive behavior trajectories in autism spectrum disorder.* Autism, 2022. **26**(1): p. 135-145.
21. Zhang, B., et al., *Effectiveness of peer-mediated intervention on social skills for children with autism spectrum disorder: a randomized controlled trial.* Transl Pediatr, 2022. **11**(5): p. 663-675.
22. Connor, A., et al., *Near-Peer Facilitation of a Soft Skills Program for Young Adults With Autism.* Am J Occup Ther, 2022. **76**(4).
23. Kent, C., et al., *Can We Play Together? A Closer Look at the Peers of a Peer-Mediated Intervention to Improve Play in Children with Autism Spectrum Disorder.* J Autism Dev Disord, 2020. **50**(8): p. 2860-2873.
24. Kent, C., et al., *Can I Learn to Play? Randomized Control Trial to Assess Effectiveness of a Peer-Mediated Intervention to Improve Play in Children with Autism Spectrum Disorder.* J Autism Dev Disord, 2021. **51**(6): p. 1823-1838.
25. Bambara, L.M., et al., *Using Peer Supports to Encourage Adolescents With Autism Spectrum Disorder to Show Interest in Their Conversation Partners.* J Speech Lang Hear Res, 2021. **64**(12): p. 4845-4860.
26. Roberts, G.J., et al., *Effects of a Self-Management with Peer Training Intervention on Academic Engagement for High School Students with Autism Spectrum Disorder.* Journal of Behavioral Education, 2019. **28**(4): p. 456-478.
27. de Nocker, Y.L. and C.K. Toolan, *Using Telehealth to Provide Interventions for Children with ASD: a Systematic Review.* Rev J Autism Dev Disord, 2021: p. 1-31.
28. Simacek, J., et al., *Current Trends in Telehealth Applications to Deliver Social Communication Interventions for Young Children with or at Risk for Autism Spectrum Disorder.* Current developmental disorders reports, 2021. **8**(1): p. 15-23.
29. Chen, Y., et al., *Extended Reality (XR) and telehealth interventions for children or adolescents with autism spectrum disorder: Systematic review of qualitative and quantitative studies.* Neuroscience & Biobehavioral Reviews, 2022. **138**: p. 104683.
30. Zhang, M., et al., *Virtual Reality Technology as an Educational and Intervention Tool for Children with Autism Spectrum Disorder: Current Perspectives and Future Directions.* Behavioral sciences (Basel, Switzerland), 2022. **12**(5): p. 138.
31. Almurashi, H., et al., *Augmented Reality, Serious Games and Picture Exchange Communication System for People with ASD: Systematic Literature Review and Future Directions.* Sensors (Basel, Switzerland), 2022. **22**(3): p. 1250.
32. Barua, P.D., et al., *Artificial Intelligence Enabled Personalised Assistive Tools to Enhance Education of Children with Neurodevelopmental Disorders-A Review.* International journal of environmental research and public health, 2022. **19**(3): p. 1192.
33. Salimi, Z., E. Jenabi, and S. Bashirian, *Are social robots ready yet to be used in care and therapy of autism spectrum disorder: A systematic review of randomized controlled trials.* Neuroscience & Biobehavioral Reviews, 2021. **129**: p. 1-16.
34. Kumazaki, H., et al., *Optimal robot for intervention for individuals with autism spectrum disorders.* Psychiatry and clinical neurosciences, 2020. **74**(11): p. 581-586.
35. Saleh, M.A., F.A. Hanapiah, and H. Hashim, *Robot applications for autism: a comprehensive review.* Disability and Rehabilitation: Assistive Technology, 2021. **16**(6): p. 580-602.

36. DiPietro, J., et al., *Computer- and Robot-Assisted Therapies to Aid Social and Intellectual Functioning of Children with Autism Spectrum Disorder.* Medicina (Kaunas, Lithuania), 2019. **55**(8): p. 440.
37. Szymona, B., et al., *Robot-Assisted Autism Therapy (RAAT). Criteria and Types of Experiments Using Anthropomorphic and Zoomorphic Robots. Review of the Research.* Sensors (Basel, Switzerland), 2021. **21**(11): p. 3720.
38. Alabdulkareem, A., N. Alhakbani, and A. Al-Nafjan, *A Systematic Review of Research on Robot-Assisted Therapy for Children with Autism.* Sensors (Basel, Switzerland), 2022. **22**(3): p. 944.
39. Rehman, I.U., et al., *Features of Mobile Apps for People with Autism in a Post COVID-19 Scenario: Current Status and Recommendations for Apps Using AI.* Diagnostics (Basel, Switzerland), 2021. **11**(10): p. 1923.
40. Wall, N.G., et al., *E-technology social support programs for autistic children: Can they work?* World journal of psychiatry, 2021. **11**(12): p. 1239-1246.
41. Maseri, M., et al., *The Implementation of Application Software to Improve Verbal Communication in Children with Autism Spectrum Disorder: A Review.* Children (Basel, Switzerland), 2021. **8**(11): p. 1001.
42. Leung, P.W.S., et al., *Effectiveness of Using Mobile Technology to Improve Cognitive and Social Skills Among Individuals With Autism Spectrum Disorder: Systematic Literature Review.* JMIR mental health, 2021. **8**(9): p. e20892.
43. Saeedi, S., et al., *Application of Digital Games for Speech Therapy in Children: A Systematic Review of Features and Challenges.* Journal of healthcare engineering, 2022. **2022**: p. 4814945.
44. Logan, K., T. Iacono, and D. Trembath, *A systematic review of research into aided AAC to increase social-communication functions in children with autism spectrum disorder.* Augmentative and Alternative Communication, 2017. **33**(1): p. 51-64.
45. Iacono, T., D. Trembath, and S. Erickson, *The role of augmentative and alternative communication for children with autism: current status and future trends.* Neuropsychiatric disease and treatment, 2016. **12**: p. 2349-2361.
46. Kasari, C., et al., *Communication Interventions for Minimally Verbal Children With Autism: A Sequential Multiple Assignment Randomized Trial.* Journal of the American Academy of Child & Adolescent Psychiatry, 2014. **53**(6): p. 635-646.
47. Donaldson Amy, L., e. corbin, and J. McCoy, *"Everyone Deserves AAC": Preliminary Study of the Experiences of Speaking Autistic Adults Who Use Augmentative and Alternative Communication.* Perspectives of the ASHA Special Interest Groups, 2021. **6**(2): p. 315-326.
48. Welch, V., et al., *Use of Mobile and Wearable Artificial Intelligence in Child and Adolescent Psychiatry: Scoping Review.* Journal of medical Internet research, 2022. **24**(3): p. e33560.
49. Black, M.H., et al., *The use of wearable technology to measure and support abilities, disabilities and functional skills in autistic youth: a scoping review.* Scandinavian journal of child and adolescent psychiatry and psychology, 2020. **8**: p. 48-69.
50. Fioriello, F., et al., *A wearable heart rate measurement device for children with autism spectrum disorder.* Scientific reports, 2020. **10**(1): p. 18659-18659.
51. Goodwin, M.S., et al., *Predicting aggression to others in youth with autism using a wearable biosensor.* Autism Res, 2019. **12**(8): p. 1286-1296.
52. Nuske, H.J., et al., *Evaluating commercially available wireless cardiovascular monitors for measuring and transmitting real-time physiological responses in children with autism.* Autism Res, 2022. **15**(1): p. 117-130.
53. Taj-Eldin, M., et al., *A Review of Wearable Solutions for Physiological and Emotional Monitoring for Use by People with Autism Spectrum Disorder and Their Caregivers.* Sensors (Basel, Switzerland), 2018. **18**(12): p. 4271.

54. Puli, A. and A. Kushki, *Toward Automatic Anxiety Detection in Autism: A Real-Time Algorithm for Detecting Physiological Arousal in the Presence of Motion.* IEEE Transactions on Biomedical Engineering, 2020. **67**(3): p. 646-657.
55. Nguyen, J., et al., *Examining the effect of a wearable, anxiety detection technology on improving the awareness of anxiety signs in autism spectrum disorder: a pilot randomized controlled trial.* Molecular autism, 2021. **12**(1): p. 72.
56. Voss, C., et al., *Effect of Wearable Digital Intervention for Improving Socialization in Children With Autism Spectrum Disorder: A Randomized Clinical Trial.* JAMA pediatrics, 2019. **173**(5): p. 446-454.
57. O'Brien, A.M., et al., *Providing visual directives via a smart watch to a student with Autism Spectrum Disorder: an intervention note.* Augmentative and Alternative Communication, 2020. **36**(4): p. 249-257.
58. Siddiqui, U.A., et al., *Wearable-Sensors-Based Platform for Gesture Recognition of Autism Spectrum Disorder Children Using Machine Learning Algorithms.* Sensors (Basel, Switzerland), 2021. **21**(10): p. 3319.
59. Brinkmann, B.H., et al., *Seizure Diaries and Forecasting With Wearables: Epilepsy Monitoring Outside the Clinic.* Frontiers in neurology, 2021. **12**: p. 690404.
60. Beniczky, S., et al., *Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology.* Clinical Neurophysiology, 2021. **132**(5): p. 1173-1184.
61. Boon-Yasidhi, V., et al., *Adverse effects of risperidone in children with autism spectrum disorders in a naturalistic clinical setting at siriraj hospital, Thailand.* Psychiatry J, 2014. **2014**: p. 136158.
62. Al-Huseini, S., et al., *Effectiveness and Adverse Effects of Risperidone in Children with Autism Spectrum Disorder in a Naturalistic Clinical Setting at a University Hospital in Oman.* Autism Res Treat, 2022. **2022**: p. 2313851.
63. Sugimoto, Y., et al., *Aripiprazole in the real-world treatment for irritability associated with autism spectrum disorder in children and adolescents in Japan: 52-week post-marketing surveillance.* BMC Psychiatry, 2021. **21**(1): p. 204.
64. Zhou, M.S., et al., *Meta-analysis: Pharmacologic Treatment of Restricted and Repetitive Behaviors in Autism Spectrum Disorders.* Journal of the American Academy of Child & Adolescent Psychiatry, 2021. **60**(1): p. 35-45.
65. Thom, R.P., et al., *Recent Updates in Psychopharmacology for the Core and Associated Symptoms of Autism Spectrum Disorder.* Current Psychiatry Reports, 2021. **23**(12): p. 79.
66. Borie, A.M., C. Theofanopoulou, and E. Andari, *The promiscuity of the oxytocin-vasopressin systems and their involvement in autism spectrum disorder.* Handbook of clinical neurology, 2021. **182**: p. 121-140.
67. Mayer, A.V., et al., *Randomized clinical trial shows no substantial modulation of empathy-related neural activation by intranasal oxytocin in autism.* Scientific reports, 2021. **11**(1): p. 15056.
68. Sikich, L., et al., *Intranasal Oxytocin in Children and Adolescents with Autism Spectrum Disorder.* N Engl J Med, 2021. **385**(16): p. 1462-1473.
69. Kruppa, J.A., et al., *Neural modulation of social reinforcement learning by intranasal oxytocin in male adults with high-functioning autism spectrum disorder: a randomized trial.* Neuropsychopharmacology, 2019. **44**(4): p. 749-756.
70. Bernaerts, S., et al., *Behavioral effects of multiple-dose oxytocin treatment in autism: a randomized, placebo-controlled trial with long-term follow-up.* Mol Autism, 2020. **11**(1): p. 6.
71. Yamasue, H., et al., *Effect of intranasal oxytocin on the core social symptoms of autism spectrum disorder: a randomized clinical trial.* Mol Psychiatry, 2020. **25**(8): p. 1849-1858.

72. Jacob, S., et al., *Efficacy and safety of balovaptan for socialisation and communication difficulties in autistic adults in North America and Europe: a phase 3, randomised, placebo-controlled trial.* Lancet Psychiatry, 2022. **9**(3): p. 199-210.
73. Hollander, E., et al., *A PHASE 2 RANDOMIZED CONTROLLED TRIAL OF BALOVAPTAN IN PEDIATRIC PARTICIPANTS WITH AUTISM SPECTRUM DISORDER.* Journal of the American Academy of Child & Adolescent Psychiatry, 2020. **59**(10, Supplement): p. S262-S263.
74. Jacob, S., et al., *Large multicenter randomized trials in autism: key insights gained from the balovaptan clinical development program.* Molecular Autism, 2022. **13**(1): p. 25.
75. Hollander, E., et al., *Balovaptan vs Placebo for Social Communication in Childhood Autism Spectrum Disorder: A Randomized Clinical Trial.* JAMA Psychiatry, 2022. **79**(8): p. 760-769.
76. Berry-Kravis, E.M., et al., *Inhibition of phosphodiesterase-4D in adults with fragile X syndrome: a randomized, placebo-controlled, phase 2 clinical trial.* Nature Medicine, 2021. **27**(5): p. 862-870.
77. Khaleghi, A., et al., *Effects of Non-invasive Neurostimulation on Autism Spectrum Disorder: A Systematic Review.* Clin Psychopharmacol Neurosci, 2020. **18**(4): p. 527-552.
78. Casanova, M.F., et al., *Translational Neuroscience in Autism: From Neuropathology to Transcranial Magnetic Stimulation Therapies.* The Psychiatric clinics of North America, 2020. **43**(2): p. 229-248.
79. Becker, J.E., E.K.B. Shultz, and C.T. Maley, *Transcranial Magnetic Stimulation in Conditions Other than Major Depressive Disorder.* Child and Adolescent Psychiatric Clinics of North America, 2019. **28**(1): p. 45-52.
80. Casanova, M.F., et al., *Transcranial Magnetic Stimulation in Autism Spectrum Disorders: Neuropathological Underpinnings and Clinical Correlations.* Seminars in pediatric neurology, 2020. **35**: p. 100832.
81. Huashuang, Z., et al., *Prevalence of Adverse Effects Associated With Transcranial Magnetic Stimulation for Autism Spectrum Disorder: A Systematic Review and Meta-Analysis.* Frontiers in psychiatry, 2022. **13**: p. 875591.
82. Robinson-Agramonte, M.L.A., et al., *Immune Dysregulation in Autism Spectrum Disorder: What Do We Know about It?* Int J Mol Sci, 2022. **23**(6).
83. Paprocka, J., et al., *Stem Cell Therapies for Cerebral Palsy and Autism Spectrum Disorder-A Systematic Review.* Brain sciences, 2021. **11**(12): p. 1606.
84. Sun, J.M. and J. Kurtzberg, *Stem cell therapies in cerebral palsy and autism spectrum disorder.* Developmental Medicine & Child Neurology, 2021. **63**(5): p. 503-510.
85. Price, J., *Cell therapy approaches to autism: a review of clinical trial data.* Molecular autism, 2020. **11**(1): p. 37.
86. Villarreal-Martínez, L., et al., *Stem Cell Therapy in the Treatment of Patients With Autism Spectrum Disorder: a Systematic Review and Meta-analysis.* Stem Cell Reviews and Reports, 2022. **18**(1): p. 155-164.
87. Hess, P., *Ethical issues cloud case report of unproven stem cell therapy for autism*, in *Spectrum*. 2021.
88. *Retraction.* Stem Cells Translational Medicine, 2021. **10**(12): p. 1717.
89. González-Domenech, P.J., et al., *A Narrative Review about Autism Spectrum Disorders and Exclusion of Gluten and Casein from the Diet.* Nutrients, 2022. **14**(9): p. 1797.
90. van der Wurff, I., et al., *A Scoping Literature Review of the Relation between Nutrition and ASD Symptoms in Children.* Nutrients, 2022. **14**(7): p. 1389.
91. Kittana, M., et al., *The Role of Vitamin D Supplementation in Children with Autism Spectrum Disorder: A Narrative Review.* Nutrients, 2021. **14**(1): p. 26.

92. Veselinović, A., et al., *Neuroinflammation in Autism and Supplementation Based on Omega-3 Polyunsaturated Fatty Acids: A Narrative Review.* Medicina (Kaunas, Lithuania), 2021. **57**(9): p. 893.
93. Tan, Q., et al., *Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation in the treatment of behavioral symptoms of autism spectrum disorder: A systematic review.* Autism Research, 2021. **14**(9): p. 1820-1836.
94. Mitchell, L.K. and P.S.W. Davies, *Pre- and probiotics in the management of children with autism and gut issues: a review of the current evidence.* European Journal of Clinical Nutrition, 2022. **76**(7): p. 913-921.
95. Deb, S., et al., *Natural Products and Their Therapeutic Effect on Autism Spectrum Disorder.* Adv Neurobiol, 2020. **24**: p. 601-614.
96. Urdaneta, K.E., et al., *Autism Spectrum Disorders: Potential Neuro-Psychopharmacotherapeutic Plant-Based Drugs.* ASSAY and Drug Development Technologies, 2018. **16**(8): p. 433-444.
97. Sissons, J.H., et al., *Calm with horses? A systematic review of animal-assisted interventions for improving social functioning in children with autism.* Autism, 2022. **26**(6): p. 1320-1340.
98. Hu, J., et al., *Art Therapy: A Complementary Treatment for Mental Disorders.* Frontiers in psychology, 2021. **12**: p. 686005-686005.
99. Shuper Engelhard, E. and M. Vulcan, *The Potential Benefits of Dance Movement Therapy in Improving Couple Relations of Individuals Diagnosed With Autism Spectrum Disorder-A Review.* Frontiers in psychology, 2021. **12**: p. 619936-619936.
100. Drüsedau, L., et al., *A structured group intervention (TüTASS) with focus on self-perception and mindfulness for children with autism spectrum disorder, ASD. A pilot study.* European archives of psychiatry and clinical neuroscience, 2022. **272**(2): p. 177-185.
101. Semple, R.J., *Review: Yoga and mindfulness for youth with autism spectrum disorder: review of the current evidence.* Child and Adolescent Mental Health, 2019. **24**(1): p. 12-18.
102. Hourston, S. and R. Atchley, *Autism and Mind-Body Therapies: A Systematic Review.* Journal of alternative and complementary medicine (New York, N.Y.), 2017. **23**(5): p. 331-339.
103. Gassner, L., M. Geretsegger, and J. Mayer-Ferbas, *Effectiveness of music therapy for autism spectrum disorder, dementia, depression, insomnia and schizophrenia: update of systematic reviews.* European journal of public health, 2022. **32**(1): p. 27-34.
104. Chen, T., et al., *Dance intervention for negative symptoms in individuals with autism spectrum disorder: A systematic review and meta-analysis.* Complement Ther Clin Pract, 2022. **47**: p. 101565.
105. Srinivasan, S.M., D.T. Cavagnino, and A.N. Bhat, *Effects of Equine Therapy on Individuals with Autism Spectrum Disorder: A Systematic Review.* Rev J Autism Dev Disord, 2018. **5**(2): p. 156-175.
106. Gabriels, R.L., et al., *Long-Term Effect of Therapeutic Horseback Riding in Youth With Autism Spectrum Disorder: A Randomized Trial.* Front Vet Sci, 2018. **5**: p. 156.
107. Rossow, T., K. MacLennan, and T. Tavassoli, *The relationship between sensory reactivity differences and mental health symptoms in preschool-age autistic children.* Autism Res, 2021. **14**(8): p. 1645-1657.
108. MacLennan, K., T. Rossow, and T. Tavassoli, *The relationship between sensory reactivity, intolerance of uncertainty and anxiety subtypes in preschool-age autistic children.* Autism, 2021. **25**(8): p. 2305-2316.
109. Hwang, Y.I., et al., *Understanding anxiety in adults on the autism spectrum: An investigation of its relationship with intolerance of uncertainty, sensory sensitivities and repetitive behaviours.* Autism, 2019. **24**(2): p. 411-422.

110. MacLennan, K., S. O'Brien, and T. Tavassoli, *In Our Own Words: The Complex Sensory Experiences of Autistic Adults.* Journal of Autism and Developmental Disorders, 2021. **52**(7): p. 3061-3075.
111. Mason, D., et al., *Predictors of quality of life for autistic adults.* Autism Res, 2018. **11**(8): p. 1138-1147.
112. Tye, C., et al., *Characterizing the Interplay Between Autism Spectrum Disorder and Comorbid Medical Conditions: An Integrative Review.* Frontiers in psychiatry, 2019. **9**: p. 751.
113. Lamy, M. and C.A. Erickson, *Pharmacological management of behavioral disturbances in children and adolescents with autism spectrum disorders.* Current Problems in Pediatric and Adolescent Health Care, 2018. **48**(10): p. 250-264.
114. Perihan, C., et al., *Effects of Cognitive Behavioral Therapy for Reducing Anxiety in Children with High Functioning ASD: A Systematic Review and Meta-Analysis.* Journal of Autism and Developmental Disorders, 2020. **50**(6): p. 1958-1972.
115. Wood, J.J., et al., *Cognitive Behavioral Treatments for Anxiety in Children With Autism Spectrum Disorder: A Randomized Clinical Trial.* JAMA Psychiatry, 2020. **77**(5): p. 474-483.
116. Bemmer, E.R., et al., *Modified CBT for social anxiety and social functioning in young adults with autism spectrum disorder.* Mol Autism, 2021. **12**(1): p. 11.
117. Yang, Y.J. and K.M. Chung, *Pilot Randomized Control Trial of an App-Based CBT Program for Reducing Anxiety in Individuals with ASD without Intellectual Disability.* J Autism Dev Disord, 2022.
118. Dickson, K.S., M.L. Galligan, and H. Lok, *Short report: A quantitative methodological review of participant characteristics in the literature testing mental health interventions for youth with autism spectrum disorder.* Autism : the international journal of research and practice, 2022. **26**(4): p. 995-1000.
119. Rodgers, J. and A. Ofield, *Understanding, Recognising and Treating Co-occurring Anxiety in Autism.* Current developmental disorders reports, 2018. **5**(1): p. 58-64.
120. Esposito, D., et al., *Sleeping without Prescription: Management of Sleep Disorders in Children with Autism with Non-Pharmacological Interventions and Over-the-Counter Treatments.* Brain Sci, 2020. **10**(7).
121. Hayashi, M., et al., *Melatonin Treatment and Adequate Sleep Hygiene Interventions in Children with Autism Spectrum Disorder: A Randomized Controlled Trial.* J Autism Dev Disord, 2022. **52**(6): p. 2784-2793.
122. Zisapel, N., *Assessing the potential for drug interactions and long term safety of melatonin for the treatment of insomnia in children with autism spectrum disorder.* Expert Rev Clin Pharmacol, 2022. **15**(2): p. 175-185.
123. Schroder, C.M., et al., *Pediatric prolonged-release melatonin for insomnia in children and adolescents with autism spectrum disorders.* Expert Opin Pharmacother, 2021. **22**(18): p. 2445-2454.
124. Halstead, E., et al., *The treatment of sleep problems in autistic adults in the United Kingdom.* Autism, 2021. **25**(8): p. 2412-2417.
125. Madra, M., R. Ringel, and K.G. Margolis, *Gastrointestinal Issues and Autism Spectrum Disorder.* Psychiatr Clin North Am, 2021. **44**(1): p. 69-81.
126. Żebrowska, P., I. Łaczmańska, and Ł. Łaczmański, *Future Directions in Reducing Gastrointestinal Disorders in Children With ASD Using Fecal Microbiota Transplantation.* Front Cell Infect Microbiol, 2021. **11**: p. 630052.
127. Kang, D.W., et al., *Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota.* Sci Rep, 2019. **9**(1): p. 5821.

128. Karhu, E., et al., *Nutritional interventions for autism spectrum disorder.* Nutr Rev, 2020. **78**(7): p. 515-531.
129. Bradshaw, J., et al., *The Use of Eye Tracking as a Biomarker of Treatment Outcome in a Pilot Randomized Clinical Trial for Young Children with Autism.* Autism Research, 2019. **12**(5): p. 779-793.
130. Kang, E., et al., *Atypicality of the N170 Event-Related Potential in Autism Spectrum Disorder: A Meta-analysis.* Biological psychiatry. Cognitive neuroscience and neuroimaging, 2018. **3**(8): p. 657-666.
131. Kala, S., et al., *Brief Report: Preliminary Evidence of the N170 as a Biomarker of Response to Treatment in Autism Spectrum Disorder.* Frontiers in psychiatry, 2021. **12**: p. 709382.
132. Ramot, M., et al., *Direct modulation of aberrant brain network connectivity through real-time NeuroFeedback.* eLife, 2017. **6**: p. e28974.
133. McPartland, J.C., et al., *The Autism Biomarkers Consortium for Clinical Trials (ABC-CT): Scientific Context, Study Design, and Progress Toward Biomarker Qualification.* Frontiers in integrative neuroscience, 2020. **14**: p. 16.
134. Steinbrenner, J.R., et al., *Patterns in reporting and participant inclusion related to race and ethnicity in autism intervention literature: Data from a large-scale systematic review of evidence-based practices.* Autism, 2022: p. 13623613211072593.
135. Smith, K.A., et al., *Disparities in Service Use Among Children With Autism: A Systematic Review.* Pediatrics, 2020. **145**(Suppl 1): p. S35-S46.
136. Luelmo, P., Y. Sandoval, and C. Kasari, *Undocumented Mexican mothers of children with autism: navigating the health care and educational service systems.* International Journal of Developmental Disabilities, 2020. **68**(4): p. 567-577.
137. Kassee, C., et al., *Physical health of autistic girls and women: a scoping review.* Mol Autism, 2020. **11**(1): p. 84.
138. Lockwood Estrin, G., et al., *Barriers to Autism Spectrum Disorder Diagnosis for Young Women and Girls: a Systematic Review.* Rev J Autism Dev Disord, 2021. **8**(4): p. 454-470.
139. Samuel, P., et al., *Sensory challenges experienced by autistic women during pregnancy and childbirth: a systematic review.* Arch Gynecol Obstet, 2022. **305**(2): p. 299-311.
140. Stedman, A., et al., *Are Children Severely Affected by Autism Spectrum Disorder Underrepresented in Treatment Studies? An Analysis of the Literature.* Journal of Autism and Developmental Disorders, 2019. **49**(4): p. 1378-1390.
141. Russell, G., et al., *Selection bias on intellectual ability in autism research: a cross-sectional review and meta-analysis.* Mol Autism, 2019. **10**: p. 9.
142. Wickstrom, J., et al., *Systematic Review: Recommendations for Rehabilitation in ASD and ID From Clinical Practice Guidelines.* Archives of rehabilitation research and clinical translation, 2021. **3**(3): p. 100140-100140.