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Review Article

An Update on Recent Advancement in Autism Spectrum Disorder Treatment Strategies

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Abstract

Utilizing technology in mental disorders studies has garnered a lot of attention recently. The quick advancement of technology has prompted researchers to use it in treatment of ASD. With so many studies being published, there is an urgent need to update doctors and researchers on the most recent developments in this area. The core of Autism Spectrum Disorder (ASD) treatment continues to be behavioral interventions, although in recent years, a number of potential targeted therapies that target the underlying neurophysiology of ASD have also become available. These have the potential to, in the future, be a standard treatment for addressing the primary symptoms of ASD, which is encouraging. The linked genetic pathways influencing ASD are anticipated to be the initial targets of treatments and potentially gene therapy in the future for ASD, even though it is likely that the development of targeted treatments will be influenced by the underlying heterogeneity in etiology. This article offers a summary of current pharmacologic therapies for ASD, including those used to treat the condition's frequent comorbidities and upcoming new treatment strategies. The Nemechek Protocol, Applied Behavior Analysis (ABA), Parent-Child Interaction Therapy, Stem Cell Therapy, Biomedical Treatment, Risperidone and Aripiprazole, Targeting Gastro Intestinal Treatment, Deep Brain Stimulation, Glutamate Receptors Treatment, Oxytocin Treatment, and readily available Herbal Treatments are some of the commonly used medications to treat the comorbidities associated with ASD.

Introduction

In 1943, Leo Kanner an Austrian-American Psychiatrist first used the term “Autism” to described the unique disorder [1]. Before autism disorder description mother were blamed of their children retardation and social impairment named as “refrigerator mothers” [2]. Autism spectrum disorder (ASD) is a multifactorial neurological disorder associated with social communications deficits [3], Impairments in the use of non-verbal communications, failures in developing age-appropriate relationships, hand flapping, finger flicking, repetitive sensory motor behaviors, interests [4] and varying intellectual disabilities [5].

According to Diagnostics and statistics manual of mental disorders (DSM-V) child with ASD have the prolonged deficits in social communications, interactions and repetitive behaviors. Mostly children with ASD are stereotyped that shows extreme distress in small changes, unusual attachment or focus on small objects, strict attachment with routines, socio-emotional reciprocity and lack of interest in social meetings, these characteristics are sufficient to meet the criteria of diagnosis DSM-V ASD [6]. DSM-IV system recognizes the five mental disorders: Rett syndrome, childhood disintegrative disorder (CDD), Asperger syndrome and pervasive development disorders and PDD-not other specified under the umbrella of PDD [7]. Researchers, neurobiologist find several faults in DSM-IV, they find that it lacks emerging conditions like internet addiction. In 2013 by updating the diagnosis standards of ASD in DSM-IV to DSM-V was published [8].

ASD is caused by several environmental and genetic factors however no single unifying cause has been elucidated yet. Autism spectrum disorder (ASD) is a neurological developmental disorder of genetic origin with a indicated heritability rate of 90% [5,7]. Ongoing research continues to improve understandings of the factors influenced in ASD. Approximately 1000 genes have been predicted to be involved in ASD based on genetic research studies. However, no single mutation has been strongly associated with ASD [9]. No single environmental or genetic factors involved in ASD, studies reported that there is likely to be 15 or more genes associated with it [7]. One of the studies reported that more than 100 genes has been associated with ASD [5]. Thus, gene linkage and genetics analysis, chromosomal variations, exome sequencing and next generations sequencing have revealed the large number of mutations and de-novo mutation associated with ASD [10]. Studies reported that parents believed that their son is traumatized or lack of mother care during pregnancy, radiations exposures effects on fetus, are the causes of ASD in their children [11]. These believed badly influenced on child-parental relationships. Most parents considered vaccinations, illness and gives more than one elucidation of ASD in their children [12]. Study reported that vaccinations and environmental factors contributed 31% and 33% respectively in the progression of ASD [13].

1 in 100 children are diagnosed with ASD all over the globe

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[14]. In US among 8-year children ASD was 1 in 54 and 2.5% was reported in children and adolescent in 2016. In Asia prevalence rate of ASD now has been increasing to 14.8 cases per 10,000 as compared to 1.9 cases before 1980 [15]. Studies reported that the prevalence of ASD varies with continent like in Asia 1.4%, Europe 0.5%, and Africa 1% and in Australia 1.7%. The prevalence of ASD varies among countries ranges from lesser like in china 0.02% to south korea 2.7% [16]. In Pakistan approximately 350,000 children suffering from ASD [17]. There is no officially database present on prevalence of ASD in Pakistan [18]. Due to heritability rate autism is considered one of the strongest genetic psychological disorders in childhood. Early detection of autism between the age of 18 months to 120 months is beneficial as it leads to initiate the process of early treatment [19]. ASD occurs in all, irrespective of racial, ethnic and socio-economic differences. In US it is investigated that Caucasian children are consistently diagnosis with ASD than black children. This may be due to differences in lack of use to health facilities and language differences. ASD diagnosis ratio in males to females is 3:1 which is higher in males than the females [20].

Treatments

Various biological and non-biological treatments are widely used interventions for ASD [21]. Studies reported that many ASD children are treated with medications, but due to associated side effects have limit their use [22]. Studies reported that parents with low education background are less successful in getting even public interventions, medications to their children that improve outcomes [3]. In this review we summarized the novel and recent advanced medical, biological, non-biological and behavioral therapies which can be used as the possible treatment for ASD in children and adolescents.

Nemechek Protocol

Dr. Nemechek published his book "The Nemechek protocol for Autism and other developmental disorders" in which Dr, discussed the possible treatment options for neurodegenerative developmental disorders. According to Nemechek different types of nutritional deficiencies, immune imbalance, oxidative stress significantly contributes in the development of ASD [23]. Nemechek found that there is an important connection between intestinal bacterial growth and brain inflammation. So, treatment of bacterial growth results in rehabilitation of brain inflammation. The Nemchek protocol is an itself rehabilitation program which involves the administration of prebiotic fiber inulin, olive oil and omega 3-fatty acids for controlling and reverse the bacterial growth and normalize the inflammatory condition within the brain [24]. AUTISTIC, CHILD, CAN, and SPORTS [25] reported that the improvement in rehabilitation process of ASD in children after the use of camel milk in combination with the Nemchek protocol, after 4-6 weeks of loose motions, their son started the healing process and improvement happens in listening process. Recent survey-based studies reported that 75% out of the total patients' respondents significantly exhibited that there is an improvement in speech and language progression. A large number of parents also satisfies with the use of Nemcheck protocol in order to reverse the autonomic dysfunctions of the brain [24].

Applied Behavior Analysis (ABA)

Applied behavior analysis recognizes significantly for the improvement in symptoms of autism, injury and other brain disorders during the past few years [26].

B.F Skinner formulated the theory of ABA and believed that responses could be established and change over time [27]. ABA requires detailed analysis of how environmental events effects on individual's behavior or the environment of individual's behavior growth [28]. ABA treatment based on learning trials and specific intervention targets [29] and it can be applied in different ways including teaching social skills, sports, daily living [30] and in natural settings [31]. ABA shows significantly better results in the behavioral intervention for childhood patients with ASD [30]. Applied, behavioral analytical training is technological, conceptually systematic, effective, and "generality" are some of the keys defining features, dimensions of the ABA defined by [32,33]. For the efficiency of ABA, it must be ensured that intervention must be comprehensive and should be start during early progression of ASD. Early and intensive behavioral intervention for children with ASD found to be effective and efficient [34]. During intervention parental support should be important and critical for children. Because parents have more closer time with their ASD children during the whole behavioral intervention program.

Effective training program for caregivers is important for high efficiency of ASD treatment. E- learning based on latest technology program should be launched for online training of the caregivers [35]. E-learning is more important during outbreak of communicable diseases such as COVD-19 recently which stuck the life for almost two years. Quality and an effective educational, training session for children and adolescent with ASD mostly reliable on ABA theory [36]. When clinicians are skilled and well-trained, ABA can be beneficial, based on a comprehensive study of the literature [34]. Vast research studies have been done on food selection and treatment of adipsia [37], by following ABA theory in children and adolescent with autism [38]. Pivotal Response Treatment (PRT) is a training more towards naturalistic behavior focused on skills and motivation and is found to be superior to ABA [29]. One of the newest additions to behaviour therapy for ASD is robot assisted therapy, which can help children with social and behavioural interaction. Children might be interested with playing robots and they can be useful as a strong therapeutic intervention for improving social behavioral and educational values in ASD children [39].

Parent-Child Interaction Therapy

Parent-Child Interaction Therapy (PCIT) is an effective technique that increase children positive behavior and improve the child-parents behavior relation. PCIT comprised of two phases, Child Directed Interaction (CDI) and Parent-Directed Interaction (PDI) [40]. Studies indicated PCIT intervention has been associated with reduction in child behavior impairments [41]. Changes in social and disruptive behavior has been observed in autism children after child directed interaction skills [42]. During CDI caregivers gives attention to child positive behavior and ignored their negative behavior, in the other phase PDI during which caregivers' trainings for the effective and command on behavior management skills [43]. PCIT is suitable for children between age of 2 to 7 years, in which child parents were characterized as a trainer to implement different home based strategies. PCIT is considered to be the gold standard strategy for the treatment of behavioral impairment disorders in children [40].

Stem Cell Therapy

In the past few years Stem Cell Therapy (STC) has been con-

sidered a useful intervention for diseases that have no cure. Stem cell therapy found to be effective, significant relief and positive effects in the ASD associated symptoms. There have been no adverse effects of SCT on patients with ASD associated symptoms [44]. Stem cells produced enzymes and release various cytokines and growth factors which may inhibit the pro-inflammatory condition in ASD children. Hematopoietic stem cell therapies increase the life-period of ASD children by delaying neuro degeneration through large enzymes production and replacement [45]. Embryonic Stem Cells (ESCs) are pluripotent and considered as an effective strategy for the treatment of ASD derived from early developmental stages of embryo. They are considered as a potential source of paracrine activity, however several ethical issues, controversies, hinder the diseases modeling by embryonic stem cell therapy [46]. Fetal stem cells derived from fetal blood, amniotic fluid, and placenta are multipotent having the ability to form in to astrocytes, neurons and oligodendrocytes. FSCs have the ability to generate various growth factors inhibit the mechanism of pro-inflammatory response make them effective for the treatment of ASD [47]. Mesenchymal stem cells (MCS) show effective results against ASD in medical research. MCSs are non-hematopoietic found in bone marrow cells, blood, fat, vascular and connective tissues. [48]. MCSs effects on a broad activity, via paracrine and trophic cellular signaling, regulate neuroinflammation, synaptic function, provides neuroprotection making them suitable for the treatment of neurological diseases including ASD [47-49]. Adipo-stem cells derived from adipose tissues and have the ability to differentiate in to different layers. ASCs are multipotent and immunosuppressive making them ideal candidates for treatment of neurological disorders, neurodegenerative diseases [47]. Studies on animal reported that there is significant improvement in ASD associated after treating with exosomes derived from adipose- MCSs [50]. Adipose-MCSs therapy showed potential improvement in the ASD symptoms, repetitive behaviors, social interaction, anxiety in the Valproic Acid (VPA)-induced autism model mice [51]. Stem cells differentiated from placenta also exhibit strong therapeutic applications, low immunogenicity and high invitro growth capacity [47]. Study reported that human cord tissue (hCT-MSCs) a product derived from umbilical cord infusion in children showed improvements in (50%) half number of participants [49]. Neural stem cells differentiated from the fetus and human brain having the extensive ability of proliferation to form other brain cells. They are multipotent cells have the capacity to generate neuron cells circuits and glial cells. NSCs mostly obtained from embryonic stem cells, MSCs and human induced pluripotent cell (hiPSCs) [52]. They are considered as neuroprotective, maintain homeostasis, repair damage cells, which makes them suitable for treatment of ASD. NSCs have been used in ASD, PDD, amyotrophic lateral sclerosis, the results are not definite as expected and still several points need to be defined like, regeneration, stabilization and prolonged survival of neurological cells after transplantation [47]. Hematopoietic stem cells HSCs are characterized by clusters of specific cell markers (CD 34, CD59, CD90 and CD 117) and derived from circulating blood, spleen, and bone marrow [53]. Due to self-resumption, mobilization of HSCs they give rise to myeloid and lymphoid linkages. HSCs suppress the altered immune response, prevent apoptosis by releasing growth factors, paracrine and bioactive molecules. Due to their ability to travel at the site of inflammation they are considered as effective therapy for the treatment of ASD disorder [53]. Induced pluripotent cells similar to the human embryonic cells regenerate differentiate in to somatic cells of various types by expressing transcriptional factors OCT4, SOX2, KLF4 and c-MYC [54] ectopically with help of integrating viruses [47]. Generating of iPSCs by lentivirus and retrovirus cause mutagenesis and leads to adverse effects for translational therapy. Various other non-integrating ways such as Sendai virus, adenovirus, synthesized RNAs and proteins for the generation of integrating free iPSCs [55]. ESCs and iPSCs are not identical as ESCs derived from inner mass cell of embryo and iPSCs start as a somatic cell without the need of embryo that possess nucleus as reprogramming factory. Gene expression signature of iPSCs is different as compared to ESCs [56]. IPSCs provides an opportunity for analyzing brain developmental disorders by invitro limitless CNS for disease pathology studies. IPSCs derived from patients suffering with wide range of diseases, AD, PD, HD, ALS, Down's syndrome, B-thalassemia used for modeling disease, toxicological diseases, regenerative medicines [57]) and drug testing [58]. IPSCs are often used in modeling diseases in the form of 2-dimensional cell cultures or 3-dimensional organoids [54].

Biomedical Treatment

Autism cannot be cured completely but several pharmacological medicinal based targeted interventions found to be effective for treating autism associated symptoms [59]. Risperidone and Aripiprazole are the two drugs approved by Food and Drug Administration (FDA)for the treatment of autism symptoms [60,61]. Medicinal treatments such as psychotics and antipsychotics such as risperidone, aripiprazole, and olanzapine [60,61] are used for the treatment of associated systems of ASD such as aggression, depression anxiety, insomnia, irritability, hyperactivity, inattention, social withdrawal [29]. The biological medicines that are approved as the treatment for Autism treat associated secondary symptoms rather than the core symptoms directly [62]. Various forms of pharmacological medications found to be effective for improving ASD related symptoms.

Risperidone and Aripiprazole

In 2006 [63] and 2009 [64] FDA approved risperidone and aripirazole for the treatment of ASD symptoms in children age of 5 or 6 years respectively. Significant improvement in behavioral symptoms of children treated with riseperidone and aripiprazole. Riseperidone and aripiprazole drugs found to be effective for the treatment of aggression, irritability and other behavioral impairments associated with ASD in children. However, both these drugs categorized as antipsychotics medications which can cause serious adverse effects such as tantrums, cardiac symptoms, metabolic effects, weight gain, fatigue, drooling, dizziness and dyskinesias [65]. Riseperidone treatment cause increase in serum prolactin level up to fourth times in children and adolescents with autism [66]. Children treated with these types of medications need serious and close monitoring [67]. Short term treatment of aggression, self-injurious behavior is possible through these types of medications. Risperidone is well effective for the short duration treatment of ASD related symptoms [68]. Aripiprazole had sales of about $7 billion in 2013, making it the largest per sale medication worldwide [69]. Aripiprazole was well tolerated and associated with improvements in targeted symptoms includes aggression, self-injurious behavior, hyperactivity and impulsivity [70], stereotype, an impairment speech in ASD [60] however their adverse effects limit their use [23]. Palmitoylethano-lamide (PEA), memantine, N-Acetylcysteine (NAC) are considered as auxiliary

treatment for management of irritability, stereotypic behavior, and hyperactivity in children and adolescents with ASD [71].

Treatments for Targeting Gastro Intestinal (GI) Factors

GI and brain communicate each other bi-directionally to regulate many biological processes [72]. Studies find that GI factors have been strongly contributed to ASDs in children and their parents and clinicians. GI disorder occur in children with ASDs varies between 9 to 91%. The common GI factors diagnoses in children associated with ASDs are constipation, diarrhea, bloody stools, vomiting [72] sleep problems, and food intolerance [73] gastro-esophageal reflux [74]. Based on understanding the pathology of GI factors in ASDs studies indicates that best treatment remains elusive [74]. The basic therapy for improving the gut microbiota symptoms associated with ASD includes, probiotics, prebiotics, herbal treatments, and Fecal Microbial Transportation (FMT) [75]. The probiotics are living organism bacteria when administered in enough amount, VISBIOME and placebo was shown effective results in the improvement of GI symptoms in ASD children. They are administered as nutritional supplements, drugs as a therapy for microbiota imbalance. Lactobacillus and Bifidobacterium are considered as prominent and common example of probiotics [76]. Studies indicated that probiotics conception was safer and showed potential health benefits in children with ASD and GI symptoms [71]. Probiotoics provide a healthier environment to gut microbiota by inhibiting harmful bacteria [77]. The gut-brain dysbiosis that is aggravating behavioral and biochemical abnormalities in autism may be treated using the Nrf2-Keap1 signalling pathway in the brain. Probiotics are possible neurotherapeutics that can inhibit the neuroinflammatory surge and target the Nrf2-Keap1/ARE pathway [78]. Probiotics improves oxytocin and serotonin level which results in the improvement of social and behavioral improvements. Galactooligopolysaccharides, starch resistant, oligosaccharides, are prebiotics which improves host bacterial strains thus improves hosts health. FMT involves the transfer of human fecal microbiota to the patient diagnoses with GI. FMT transportation contain thousands of bacterial species better than the probiotics which constitutes only few bacterial species [79]. Microbiota Transfer Therapy (MTT) an advanced technique of FMT has gained much more attention. High initial dose of standardized human gut microbiota is used in an FMT for 7-8 weeks after a 2-week antibiotic treatment, followed by stool cleansing. Studies indicated that MTT showed potential for improving diarrhea, constipation, and abdominal digestion [80].

Deep Brain Stimulation (DBS) in ASD

In 1985 non-invasive intervention for the treatment of neurological disorders was developed by Barker [79]. Transcranial Magnetic Stimulation (TMS) work on the mechanism of faraday's law of electromagnetic induction, is an emerging noninvasive tool for better understandings of etiology related to ASD and other neuropsychiatric disorders. Transfer of high intensity current through the coil it induces magnetic current. The magnetic field generates stimulation which excites or inhibits the cortical neurons [80]. TMS has been categorized in to three forms, single pulse, paired pulse, and repetitive (rTMS) [81]. Single pulse (sTMS) in which single pulse of current is applied to modulating cortical excitability of neurons, paired pulse (ppTMS) in which two pulses is applied at the fixed frequency through same coil Repetitive Transcranial Magnetic Stimulation (rTMS) has been considered as a therapeutic intervention for psychiatric disorders including stroke, Parkinson's disease, Alzheimer disease, epilepsy and associated symptoms of ASD [82]. Studies indicated that further clinical trials needed to investigate the therapeutics effects of TMS in Autism patients [83]. In 1997, DBS was first approved by FDA in which electrical impulses by using electrodes targets the specific regions of the brain. It is non-invasive technique to treat patients when medications are no prolonged effective and has been widely used in the treatment of Parkinson's disorder, psychiatric disorders, depression, obsessive compulsive disorder, seizure disorder, Tourette syndrome, reducing obsessive compulsive symptoms associated with ASD and aggressive behavior [83]. Self-injurious behavior such as self-biting, self-cutting, self-scratching, hair pulling, head hanging, cause serious health risk for patient health [84]. DBS is a surgical intervention that regulates brain circuits and improves self-injurious behavior, mood, anxiety, behavior, psychiatric symptoms [84] and social communication using by electric impulses [85]. Children and adults who had followed an intervention of DBS showed improvement in repetitive behaviors. Studies indicated that DBS could be useful therapy for improving aberrant behaviors in ASD includes crying, irritability, lethargy and unplanned criminal activities. Neuroscientist's hope continues that DBS could be the effective for improving the life of patients [84].

Treatments Targeting Glutamate Receptors

Glutamate is a neurotransmitter that has been directly played a major role in cognitive functions such as learning, memory [86] synaptic plasticity, and brain circuit formation [87]. Glutamate receptors are divided in to two types' ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). Ionic glutamate receptors are gated ion-channels that mediate fast excitory neurotransmission in the nervous system. Alteration in iGluRs leads to psychiatric and neurological disorders [88]. Metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors facilitating chemical synapses [89]. The imbalance between excitatory and inhibitory commonly proposed mechanism in ASD and ASD co-morbidity epilepsy [90]. The GABA (Amino butyric acid) switch, also recognized as shifting of GABA activity in neurons, has been considered to be the cause of the excitory-inhibitory imbalance. GABA switch may be dependent on a decrease in intracellular chloride. Bumetanide administration associated with reduction in the GABA/Glutamine-Glutamate ratio, thus reduced the severity of symptoms such as communication and cognitive abilities [91] associated with ASD [92]. Increased in neurotransmission at N-methyl-D-Asparate (NMDA) glutamate receptor has been associated in social, communications etiologies and irritability in ASD. The agonists and antagonists' agents such as amantadine, memantine, dextrometorphan, lamotrigine, D-cycloserine, N-acetylcysteine, basimglurant, fenobam, mavoglurant [93] used to counteract hyperactivation in altered glutamate signaling in ASD [94]. Memantine agents are well tolerated have low risk of side effects. Riluzule a drug with limited side effects increases the inhibitory effect of prefrontal cortex without disrupting glutamine in ASD patients [93].

Intranasal Oxytocin Treatment

Oxytocin is a hormone produced in the hypothalamus release in the blood through pituitary glands. Autism associated with genetic origin disease and miR-6126 targets genes in oxytocin signaling pathway, suppress the stimulation and the variants in oxytocin receptors such as rs7632287, rs237887, rs2268491, and rs2254298, rs2254298 and rs53576, influenced the activ-

ity of intranasal oxytocin facilitating in social cognition symptoms associated with ASD [95]. Oxytocin administration via -intranasal route were potential intervention for improvement of social symptoms related to ASD. Studies indicated that intranasal oxytocin therapy results in improvement were noted in both the social communication and irritability [96]. Analysis of previous studies reported that intranasal oxytocin therapy well tolerated and probably the possible treatment in ASD patients. However, studies indicated further clinical investigations are recommended to investigate the effectiveness and adverse effects of intranasal treatment [97].

Herbal Treatments

Due to limited efficacy and various adverse side effects of biomedical treatments herbal medicines are considered as an alternative for treating neurophysiological disorders. Studies reported that medicinal plants such as Zingiber officinale, Camellia sinensis, Piper nigrum, Curcuma longa, Bacopa monnieri, Glycine max, Prunus dulcis, Ginkgo biloba [98], Arthrospira platensis and Chlorella vulgaris have antioxidant activity [99]) and neuroprotective effects and considered as a beneficial for treating symptoms associated with autism disorder [100]. Cannabinoids also found to be effective therapeutics for treating major symptoms of ASD such as social behavior, aggression, self- injurious behavior, anxiety and sleep disorders [101] and associated comorbidities [102]. Plants based drugs are bioactive molecules such as luteolin [103], cannabinoids, flavonoids, curcuminoids, piperine, resveratrol, and bacosides are considered an effective pharmaceutical to reverse the symptoms associated with ASD such as behavioral conditions with no side effects as compared to neuropsychiatric strategies [104]. A famous medicinal plant in south korea named as Korean Red Ginseng (KRG) have been gaining importance of scientists due to its positive impacts in treating neurological disorders. Long term use of KRG improves the behavioral ASD deficits in mice [105].

Discussion

ASD is a complex disorder with multi-associated comorbidities. As throughout this review, a multitude of research articles related to effectiveness of various psychological and biological treatment. Although ASD cannot be totally treated, the underlying abnormalities can be controlled and reduced. Neuroscientists continues to research and refines further these techniques to improve the early detection therapies in children and adolescents associated with ASD [28]. Among the various pharmacological treatment used for treatment of ASD associated symptoms only Risperidone and Aripiprazole drugs are approved by FDA. Psychological behavioral therapies are considered as a first line treatment with pharmacological and stem cells therapies aided to improve patient conditions in daily life activities [106].

Parents with less educational background are not successful to obtained specialized or even funded intervention that could improve results in children as compared to educated families [4]. Research indicates that stem cell therapy improves symptoms and suitable for patients with no adverse side effects [44]. The development of authentic clinically useful biomarkers for risk assessment, diagnosis, forecasting clinically relevant subgroups, and treatment success strongly linked with the future of ASD biomarker research [107,108]. Use of technologies and bioengineering based robotics devices are need of the time to treat and improving neurological development diseases in children and adults as it is less time consuming and convenient.

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