SZPERNALOWSKA, Anna, MATSHABA, Vimbisoyashe Ivy, MRUGAŁA, Karolina, CHOINKA, Martyna, KALISIAK, Jakub, MATACZYŃSKA, Anna and PAPROCKI, Michał. Autism Spectrum Disorder: Latest Advances in Treatment. Quality in Sport. 2024;22:54744 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.54744
https://apcz.umk.pl/QS/article/view/54744

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.08.2024. Revised: 17.09.2024. Accepted: 21.09.2024. Published: 24.09.2024.

Autism Spectrum Disorder: Latest Advances in Treatment

Anna Maria Szpernalowska
Warsaw Southern Hospital
Rotmistrza Witolda Pileckiego 99, 02-781 Warsaw, Poland
aslowinska98@gmail.com
https://orcid.org/0009-0008-2016-5300

Vimbisoyashe Ivy Matshaba
University Clinical Hospital in Poznan
Długa 1/2, 61-848 Poznan, Poland
vmatshaba3@gmail.com
https://orcid.org/0009-0001-2219-2774

Karolina Mrugała
University Clinical Hospital in Poznan
Długa 1/2,61-848 Poznan, Poland
karmru12@wp.pl
https://orcid.org/0009-0005-0153-595X

Martyna Choinka
University Clinical Hospital in Poznan
Przybyszewskiego 49, 60-355 Poznan, Poland
m.choinka@op.pl
https://orcid.org/0009-0005-0951-3368

Jakub Kalisiak
Independent Public Complex of Health Care Facilities of the Ministry of Interior and Administration in Poznan
Dojazd 34, 60-631 Poznan, Poland
kubakalisiak@gmail.com
https://orcid.org/0009-0000-2472-3148

Anna Mataczyńska
Lazarski University, Faculty of Medicine
Świeradowska 43, 02-662 Warsaw, Poland
ania.mataczynska12@gmail.com
https://orcid.org/0009-0005-7643-6614

Michał Paprocki
Lazarski University, Faculty of Medicine
Świeradowska 43, 02-662 Warsaw, Poland
michalp98@onet.pl
https://orcid.org/0000-0002-9480-5090

Abstract

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition marked by deficits in social communication and the presence of restricted, repetitive behaviours. Despite the global prevalence of ASD, its diagnosis and treatment remain challenging due to the absence of specific biomarkers and the heterogeneity of symptoms. ASD is incurable and current management options aim to minimize the symptoms and maximize the patients' ability to function. There is no one standardized treatment for ASD at present, recommended medical interventions involve various therapies which include cognitive behavioral therapy alongside additional personalized pharmacological symptomatic treatments. New approach for ASD management includes sensory integration therapy (SIT) as well as dietary interventions, like gluten-free, casein-free and ketogenic diets. Other innovative treatment strategies are targeted at gut microbiome and include probiotic treatment and fecal microbiota transplant. In this review possible genetic variants associated with ASD are discussed as well as their influence on the manifestation and management of clinical symptoms. For a better understanding on how genetic variables impact drug effectiveness in individuals and the importance of pharmacogenetics in ASD. This paper aims to explore the available and possible treatment options as well the genetic components associated with ASD. In summary, this paper reviews the current and emerging treatment options for ASD.

Keywords: "autism spectrum disorder", "treatment strategies", "sensory integration therapy", "diet treatment", "genetics", "pharmacogenetics"

Introduction

Autism Spectrum Disorder (ASD) is a condition characterized by varying symptoms such as deficits in social communication as well as restricted, repetitive or atypical sensory-motor behavior [1]. These disorders appear at an early stage of child's development with diagnosis taking place at various stages of the patient's life. This is primarily due to diagnostic challenges associated with the lack of disease-specific biomarkers, varying severity ranging

from very mild to severe in addition to clinicians relying solely on the child's behavior caused by [2]. The cause of the disorder is heterogeneous, attributed to genetics but also to the interplay of other factors influencing abnormalities in brain development and neuronal reorganization [3]. According to data from the World Health Organization (WHO), currently 1 in 100 children worldwide has autism spectrum disorder. Due to the scale of its prevalence, awareness and knowledge of autism spectrum disorder has significantly increased over the past few decades [4]. This has led to the initiation of numerous studies aiming to find the "golden therapy" for patients who require constant care and are unable to be independent throughout their lives.

Current Treatments and Intervention for Autism Spectrum Disorder

Currently available treatment methods involve cognitive behavioral therapies alongside additional personalized pharmacological symptomatic treatment. Parents are taught how to cater for their children with emphasis on creating conducive environments for the children to slowly take initiative. In cases of children with significant intellectual delay parents should avoid initiating tasks instead they can take on an open verbal and expressive role. Every milestone achieved allows parents to positively cope and it also influences progressive child's development [2]. Therapist conducted cognitive behavioral therapies one-on-one with the patient allows speech and other cognitive skill development. These can be conducted in group settings for both parents and children with anxiety reduction a predominant occurrence in children with ASD as a focal point [5]. Pharmacological treatment aims to address behavioral comorbidities. Atypical neuroleptics and serotonin and dopamine receptors antagonists risperidone and aripiprazole are commonly prescribed. Their action on neurotransmitters reduces agitation and irritability [6,7]. In case of iatrogenic obesity associated with their use, metformin can be used as the treatment of choice [8]. Methylphenidate is used in the treatment of patients with ADHD, however for epilepsy, anxiety and mood disorders the recommended pharmacotherapy is the same as for patients without ASD [9]. Present-day treatment approaches do not cure ASD but focus mainly on minimizing and in some cases eliminating symptoms so that the patients become as independent as possible.

Sensory integration therapy

Sensory integration therapy (SIT) is a treatment approach based on Ayres' theory (1972), which suggests that behavioral problems in children with ASD result from a limited ability to process and integrate sensory events [10]. Atypical sensory reactivity may be key to many behavioral abnormalities in these patients, hence prompting a thorough assessment of sensory functions in children with ASD [11]. In 2013, sensory-related disorders associated with hyperreactivity or hyporeactivity were included as diagnostic criteria in DSM-5 (American Psychiatric Association, 2013) [12]. Moreover, in 2021, Ayres' approach to sensory integration was recognized as an evidence-based practice by the National Clearinghouse for Autism Evidence and Practice (NCAEP) [13]. SIT involves trying to organize the sensory system through stimuli that stimulate auditory, tactile, vestibular, and proprioceptive receptors. During sessions, special equipment is used, which can be in the form of balls, swings, weighted vests, cushions, etc. [14]. Tests conducted on a group of autistic individuals of the same age, examining the issue of sensory processing assessed on the SCOPE scale, demonstrated that the intervention group showed significantly greater improvement in all areas except for the factor "emotional reactivity." The study revealed that SIT can improve occupational performance and the ability to process sensory information in children with ASD. Therefore, therapists may consider it effective in improving social skills and subsequently the child's health [15]. It has also been proven that sensory integration positively affects the well-being of patients and their families [16]. It helps parents better understand their children's behavior, problems related to their behavior, and it also teaches them how they can be of support resolving them daily [17]. Studies have emphasized the positive impact of SIT on the development of patients' learning abilities [18]. There have been discussions on the significance of sensory integration therapy in the development of emotional intelligence [19], as well as its effectiveness in alleviating emotional and behavioral problems [20, 21]. The key in this case is the improvement in communication, socialization, and daily living skills of patients [22]. Sensory integration therapy contributed to improved motor function in the study patients [23]. Sensory integration of autistic children has also been proven to reduce stereotypic behavior by seeking a particular aspect of stimulation, which maps a positive effect on reducing stereotypic behavior [24]. Some studies also highlighted the lack of sufficient evidence on SIT's effectiveness, with emphasis on the low methodological quality in studies that showed a positive impact of SIT. After an increase in the quality of conducted analyses, achieved outcomes showed a tendency towards negative results [25]. There is also interest in the cost-effectiveness of sensory integration. Sensory integration therapy is more costly compared with usual care alone. According to some

studies, SIT does not demonstrate clinical benefit above standard care. Subgroup effects are hypothesis-generating only, and there is insufficient evidence to confirm this thesis [26].

Gluten-free, casein-free and ketogenic diet

It has been proven that patients diagnosed with ASD frequently suffer from gastrointestinal symptoms [27]. Moreover, a correlation was observed between intensity of the digestive problems and the increase in anxiety and sensory sensitivity in children with ASD [28]. Higher concentrations of Clostridium spp. and their toxins were revealed in ASD patient's contrary to healthy individuals [29]. Studies conducted on siblings confirmed that ones with ASD have a higher tendency to constipation than their healthy brothers and sisters [30].
The gut microbiome is one of the most promising areas of science today. Importance of gut-brain axis in etiology and symptoms of ASD is constantly under research. Diets suggested so far are still controversial and the evidence of their positive influence is mainly relevant for improvement in behavioral responses, while the mechanisms and the physiological consequences are unclear. Despite this ambiguity, however, some groups of ASD patients may benefit from using an appropriate diet [31].

One theory identifies the excess of opioids as the probable cause,in particular, because casein and gluten are the source of opioid peptides. It is believed that incomplete breakdown of proteins to amino acids leads to generation of gluteomorphin and casomorphin. Those peptides enter the bloodstream due to excessive intestine wall permeability which is often observed in patients with autism and then with blood they get to the central nervous system. Those molecules, structurally like opioids, activate opioid receptors in the brain [30].

So far, the significance of this pathway in ASD etiology has not been proven, even though the urine of individuals who follow a gluten-free diet contained lower peptide concentrations and people from this group experienced alleviation of gastrointestinal symptoms [32]. Moreover, innate disruption of immune system activity, which may result in excessive immune response to mild environmental factors, such as dietary proteins [33]. Studies revealed that 87% children with autism diagnosis and concurrent gastrointestinal symptoms have elevated levels of anti-gliadin antibodies and 90% of them have increased anti-casein antibodies

[30]. The earlier mentioned gliadin, which is a glycoprotein found in gluten, induces higher leakage of macromolecules through intestinal wall [34].

However, despite the rising number of theories supporting the introduction of casein-free and gluten-free diets, earlier investigation of the physiological effects of exclusion of so many food components is crucial. It is important to ensure that those dietary patterns do not have a negative influence on the gut microbiome of autistic patients, which is inherently impaired, through elimination of favorable microbes and growth of the opportunistic ones [35]. Opponents of this solution point out the elimination of the sources of fiber from the diet, which may worsen the symptoms of constipation and even lead to malnutrition. The latter may result in suppression of bone formation and production of neurotransmitters with the risk of enhancement of behavioral problems [30]. Currently, literature and studies which are disqualified because of methodological limitations do not enable to determine whether introducing a casein-free or gluten-free diet is efficient [36]. Present state of knowledge only allows to recommend elimination diets in case of diagnosed intolerances to allergens contained in food [30].

A ketogenic diet (KD), characterized by high fat content, mobilizes the body to use fat as a source of energy, which positively affects metabolic/mitochondrial disturbances and epileptic fits. Laboratory studies in mice have shown evidence of favorable influence on neuronal processes, formation of myelin and white matter, which may contribute to alleviation of ASD symptoms [37]. Additionally, normalization of gut microbiome constitution with reduction of its abundance was observed, which would explain the easing of the neurological manifestations [38]. KD increases gut microbial diversity, due to elevation in production of butyrate, which is associated with decreased levels of pro-inflammatory cytokines. Moreover, KD lowers brain-derived neurotrophic factor (BDNF) levels and alters levels of BDNF-associated miRNAs in the plasma, which impact brain activity through epigenetic pathways [39]. It was shown, however, that KD may lead to many adverse effects, including constipation and gastroesophageal reflux disease. Abovementioned illnesses have an inflammatory origin of which risk is elevated while following KD [40].

Since emergence of ASD is linked to inflammation, oxidative stress, immunological dysfunction and mitochondrial malfunction, the new dietary approach to autism targets consumption of polyphenols. Implementation of resveratrol (RES), which is a natural plant antitoxin, decreases levels of ROS and neuroinflammation by activating silent information regulator-1 (SIRT-1). Studies show that upregulation of SIRT-1 has a neuroprotective effect in

ASD due to lowering NF- κB mediated neuroinflammation. The clinical effect observed in animal models is alleviated social impairment and stereotyped activity as well as improved hyperactivity, anxiety and cognitive function [41, 42].

At present none of the diets is routinely recommended for children diagnosed with autism, but they set out on a path toward a non-invasive treatment and research for less restrictive efforts aiming at improvement of patient's microbiome [43].

Probiotic treatment and fecal microbiota transplant

Recently, much study has been done concerning the role of bidirectional gut-brain axis in the pathogenesis of diseases, starting from depression, anxiety and irritable bowel syndrome and ending with the neurodevelopmental disorders, such as ASD. Studies in animals have shown that bacterial colonization of intestines has a significant influence on the development of central nervous system and enteric nervous system [44]. Trials using western eating patterns indicated that this type of diet promotes inflammation, which has a negative impact on behaviour and anxiety [45]. However, high polyunsaturated fats intake may alleviate depression [46].

Progress in scientific research enabled observation of positive influence of treatment with probiotics and prebiotics. By optimizing gut microbiome, they have a beneficial influence on improvement of coexisting ASD symptoms [47]. Probiotics are living microorganisms that are intended to have health benefits through restoring the gut microbiota. A study conducted on the maternal immune activation (MIA) mouse model proved that Bacteroides fragilis oral therapy regulates gut permeability, changes the microbiological composition of intestinal content and improves behavioral problems in ASD. In the same experiment 4-ethylphenyl sulfate (4EPS) was used to trigger behavioral disorders in mice. 4EPS is a metabolite derived from microbiota, which further confirms the participation of gut microbiota in ASD pathogenesis [48]. In another experiment on mice, maternal high-fat diet (MHFD) was applied, inducing intestinal dysbiosis in offspring and accompanying social dysfunctions. Subsequently, L. reuteri bacterial strain was administered as a part of a therapy and resulted in correction of oxytocin levels and behavioral deficits [49]. In study conducted on 15 autistic participants, implementing oral SB-121, a combination of L. reuteri, dextran microparticles and maltose administered once daily for 28 days, resulted in improvements in adaptive behavior measured

by Vineland-3 Adaptive Behavior Composite score and social preference as measured with eye tracking. SB-121 was safe and well tolerated with no serious adverse events [50]. Another study investigating the influence of L. reuteri showed that its strains ATCC-PTA-6475 and DSM-17938 improve social functioning in children with autism without affecting autism severity or repetitive behaviors. In a mouse model only the 6475 strains reversed the social deficits. However, further research on strain-specific effects is needed [51].

Prebiotics include inulin, fructooligosaccharides, galacto-oligosaccharides and lactulose. Those selectively fermented, non-digestible components promote change in the composition or/and activity of intestinal microbiome [47]. Studies dedicated to supplementation of oligosaccharides revealed their inductive impact on Lactobacilli and Bifidobacteria growth as well as neurotrophic effect [52]. Subsequent research has shown that galacto-oligosaccharides intake suppresses neuroendocrine response to stress [53]. 6-week Bimuno® galactooligosaccharide (B-GOS®) prebiotic intervention combined with gluten and casein-free diet in 30 autistic children, showed a significant improvement in social skills, decrease in anti-social behaviours and changes in intestinal microbiome composition [54].

Another method of treatment which is being investigated is fecal microbiota transplant (FMT). Compared with probiotics, which contain only a few bacteria species, FMT comprises about a thousand species of bacteria and is applied in treatment of various gastrointestinal tract disorders [55]. The scientists see the potential of FMT in ASD treatment, due to its capability to rebalance the gut microbiome. The latest research shows that FMT leads to decrease in the scores of Autism Behavior Checklist (ABC), Social Responsiveness Scale (SRS) and Childhood Autism Rating Scale (CARS), which indicates that FMT clinically improves ASD symptoms. Additionally, the improvement may be greater with the number of courses of FMT treatment [56]. However adverse effects of the therapy were also noticed, since there are many undetermined microbes in the gut which may be pathogenic while being introduced to the host's intestinal system. Hence, to minimize the risk, strict donor screening is needed [57].

Microbiota transfer therapy (MTT) is a method similar to FMT, however MTT involves preparation by antibiotic treatment, a bowel cleanse, a stomach acid suppressant, preceding the FMT procedure [58]. In the study consisting in 8-week MMT therapy, significant improvement of digestive problems and behaviors typical for ASD was observed in 16 out of 18 children, which persisted at least 8 weeks after treatment. MTT had a favorable effect on gastrointestinal problems, by decreasing approximately 80% symptoms of constipation, diarrhea, indigestion, and abdominal pain. It also resulted in improvement of SRS, ABC, CARS and Parent Global

Impressions-III (PGI-III) scores [59]. Interestingly, a follow-up with the same 18 participants two years after abovementioned treatment, resulted in the maintenance of the positive effect on digestive symptoms and even greater improvement of ASD symptoms, accompanied by favorable changes in gut microbiome [60]. These findings further confirm the positive influence of microbiota-targeted therapies and their long-term safety and efficacy.

Currently the role of the intestinal microbiome in pathogenesis of ASD remains unclear and therefore it is important to thoroughly investigate the immune, neuronal and hormonal pathways in the gut-brain axis. Additionally, clarification of the differences in observed microbiological changes in patients with ASD is crucial. It is essential to study the safety of using probiotics and FMT in animal models and humans as well as analyze the effects of implementing various symbiotic species and their metabolites [61].

Genetic Testing - Pharmacogenetics

Many studies have shown that the pathogenesis of autism spectrum disorder has a genetic component. At the same time, they indicate the involvement of hundreds of gene variants with variable effects that lead to manifestations of diversified ASD symptoms [62]. Various genome mutations are detected, from single-nucleotide deletions, insertions to changes involving thousands of base pairs. De novo mutations account for a larger percentage of the genome mutation variants [63][64]. Multiple rare gene variants are also contributors associated with ASD and they still require further exploration [64]. Ongoing genetic research have highlighted genetic variants associated with ASD, taking its diagnosis beyond behavioral changes as the key diagnostic tool. Having a better understanding of the underlying mechanisms will help tailoring optimized treatment which will ensure enhanced clinical outcomes and patients' quality of life [65].

Gene penetrance is pivotal in determining phenotypic frequency, expressivity as well as the intensity of clinical manifestations of a given genetic variant. In order to make a definitive diagnosis, parents' genetic assessment and evaluation whether the patient's results significantly deviate from the expected results is highly recommended in cases of newly detected de novo mutations [66]. Gender plays a role in the risk of autism spectrum disorder, women showed greater resistance to mutational implications associated with ASD [67, 68]. Additional implications are introduced by wide phenotypic pleiotropy. The scope of children with ASD

includes various degrees of intellectual disability, epilepsy, attention deficit hyperactivity disorder, concomitant somatic diseases. Therefore, full range phenotype detection will be pivotal in the clinical management of comorbidities since it will enable surveillance and early intervention in the event of increased risk associated with having a specific mutation [69].

The aim of genetic testing is to find correlation between a given genotype and its sensitivity to given pharmacological compounds, for example rapamycin admission targets are Tuberous sclerosis 1(TSC1), Tuberous sclerosis complex 2 (TSC2), phosphatase and tensin homolog (PTEN), Neurofibromatosis type 1(NF1) mutations [65]. In pharmacogenetic testing, the focus is on the patient's response to treatment and the possible occurrence of side effects. This is important in assessing whether a given drug brings more benefits than harm which is crucial in optimizing therapy for the patient. Most pharmacogenetic studies focus on antipsychotics, antidepressants and stimulants due to their common use in children with ASD [70][71]. A J T MacCracken et al study showed that patients with specific genetic variants have better response to methylphenidate treatment [72].

The essence of genetic research is to acquire better understanding of pathomechanisms of ASD.A research based on mice with PTEN mutations was conducted to detect changes in neurodevelopmental processes in patients with this genetic variant. The study showed the importance of PTEN during neurogenesis as well as the associated behavioral abnormalities between PTEN-ASD patients and Pten cKO mice studied. Comprehensive analysis is still required in order to understand the pathomechanism behind PTEN-ASD [73]. Further knowledge of the pathophysiology of ASD and its association with mutations would allow breakthroughs in optimizing treatments.

Presently, there are many obstacles in the way for patient tailored treatments, mostly because genetic diagnostics is only conducted in cases of co-occurrence between intellectual disabilities and somatic disorders which in turn slows down data surveillance of new genotypes and clinical manifestations. This also reduces information and knowledge accessibility for both the family and medical staff providing care for the patient. Increasing financial outlays could increase the overall number of people genetically tested, which would enable obtaining comprehensive data about rare variants leading to the discovery of new associated genes[74].

Due to the scarcity of resources, genetic testing is inaccessible in many developing countries [75].

Summary

In recent years we have observed a rapid increase regarding ASD diagnosis and treatment. The reason behind the great involvement of many scientists is because ASD is becoming more and more common within the general population. Research is focusing on determining safety and effectiveness regarding new therapies, from less invasive sensory therapies and restrictive dietary approaches to targeted therapies. Scientists are particularly expectant about genetic testing since the results will allow creating patient-based treatment models. This would enhance the therapeutic effect of pharmacotherapy and also reduce the occurrence of adverse events in ASD comorbidities treatment. The latest evidence on new treatments is insufficient in order to implement them into clinical practice. However, further research based on current achievements may provide instrumental aid in increasing the efficiency of therapy for children with ASD in the future.

Disclosure:

Authors'contribution:

Conceptualization: Vimbisoyashe Ivy Matshaba, Martyna Choinka

Methodology: Karolina Mrugała, Michał Paprocki

Software: Martyna Choinka, Karolina Mrugała,

Check: Anna Maria Szpernalowska, Jakub Kalisiak

Formal Analysis: Vimbisoyashe Ivy Matshaba, Anna Mataczyńska

Investigation: Karolina Mrugała, Anna Maria Szpernalowska, Michał Paprocki

Resources: Martyna Choinka, Michał Paprocki

Data Curation: Karolina Mrugała

Writing-Rough Preparation: Karolina Mrugała, Jakub Kalisiak

Writing-Review and Editing: Anna Maria Szpernalowska

Visualization: Vimbisoyashe Ivy Matshaba, Karolina Mrugała,

Supervision: Anna Maria Szpernalowska, Martyna Choinka, Anna Mataczyńska

Project Administration: Anna Maria Szpernalowska, Vimbisoyashe Ivy Matshaba, Karolina Mrugała, Martyna Choinka, Jakub Kalisiak, Michał Paprocki, Anna Mataczyńska

All authors have read and agreed with the published version of the manuscript.

Funding statement:
The study did not receive special funding.
Institutional review board statement:
Not applicable.
Informed consent statement:
Not applicable.
Data availability statement:
Not applicable.
Conflict of interest:
The authors declare no conflict of interest.

References:

1. Leekam SR, Prior MR, Uljarevic M. Restricted and repetitive behaviors in autism spectrum disorders: a review of research in the last decade. Psychol Bull. 2011;137(4):562-593. doi:10.1037/a0023341

2. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018;392(10146):508-520. doi:10.1016/S0140-6736(18)31129-2

3. O'Reilly C, Lewis JD, Elsabbagh M. Is functional brain connectivity atypical in autism? A systematic review of EEG and MEG studies. PLoS One. 2017;12(5):e0175870. Published 2017 May 3. doi:10.1371/journal.pone.0175870

4. World Health Organization, Autism. 2023. https://www.who.int/en/news-room/fact-sheets/detail/autism-spectrum-disorders (Access: 19.08.2024)

5. Schreibman L, Dawson G, Stahmer AC, et al. Naturalistic Developmental Behavioral Interventions: Empirically Validated Treatments for Autism Spectrum Disorder. J Autism Dev Disord. 2015;45(8):2411-2428. doi:10.1007/s10803-015-2407-8

6. Maneeton N, Maneeton B, Putthisri S, Woottiluk P, Narkpongphun A, Srisurapanont M. Risperidone for children and adolescents with autism spectrum disorder: a systematic review. Neuropsychiatr Dis Treat. 2018;14:1811-1820. Published 2018 Jul 11. doi:10.2147/NDT.S151802

7. Bartram LA, Lozano J, Coury DL. Aripiprazole for treating irritability associated with autism spectrum disorders. Expert Opin Pharmacother. 2019;20(12):1421-1427. doi:10.1080/14656566.2019.1626825

8. Handen BL, Anagnostou E, Aman MG, et al. A Randomized, Placebo-Controlled Trial of Metformin for the Treatment of Overweight Induced by Antipsychotic Medication in Young People With Autism Spectrum Disorder: Open-Label Extension. J Am Acad Child Adolesc Psychiatry. 2017;56(10):849-856.e6. doi:10.1016/j.jaac.2017.07.790

9. Sanchack KE, Thomas CA. Autism Spectrum Disorder: Primary Care Principles. Am Fam Physician. 2016;94(12):972-979.

10. Ayres, A. Jean. Sensory integration and learning disorders. Western Psychological Services, 1972.

11. Posar A, Visconti P. Sensory abnormalities in children with autism spectrum disorder. J Pediatr (Rio J). 2018;94(4):342-350. doi:10.1016/j.jped.2017.08.008

12. Vahia VN. Diagnostic and statistical manual of mental disorders 5: A quick glance. Indian J Psychiatry. 2013;55(3):220-223. doi:10.4103/0019-5545.117131

13. Hume K, Steinbrenner JR, Odom SL, et al. Evidence-Based Practices for Children, Youth, and Young Adults with Autism: Third Generation Review [published correction appears in J Autism Dev Disord. 2023 Jan;53(1):514. doi: 10.1007/s10803-022-05438-w]. J Autism Dev Disord. 2021;51(11):4013-4032. doi:10.1007/s10803-020-04844-2

14. Section On Complementary And Integrative Medicine; Council on Children with Disabilities; American Academy of Pediatrics, Zimmer M, Desch L. Sensory integration therapies for children with developmental and behavioral disorders. Pediatrics. 2012;129(6):1186-1189. doi:10.1542/peds.2012-0876

15. Kashefimehr B, Kayihan H, Huri M. The Effect of Sensory Integration Therapy on Occupational Performance in Children With Autism. OTJR (Thorofare N J). 2018;38(2):75-83. doi:10.1177/1539449217743456

16. Randell E, McNamara R, Delport S, et al. Sensory integration therapy versus usual care for sensory processing difficulties in autism spectrum disorder in children: study protocol for a pragmatic randomised controlled trial. Trials. 2019;20(1):113. Published 2019 Feb 11. doi:10.1186/s13063-019-3205-y

17. Krupa-Kotara K, Kosiorz M, Barylska K, Grajek M. Sensory integration disorders in children with autism spectrum disorder—A review study. Applied Psychology Research. 2023; 2(1), 548. https://doi.org/10.59400/apr.v2i1.548

18. Vives-Vilarroig J, Ruiz-Bernardo P, García-Gómez A. Sensory integration and its importance in learning for children with autism spectrum disorder. Cadernos Brasileiros de Terapia Ocupacional. 2022; 30, e2988. https://doi.org/10.1590/2526-8910.ctoAR22662988
19. Pergantis P, Drigas A. Sensory integration therapy as enabler for developing emotional intelligence in children with autism spectrum disorder and the ICT's role. Brazilian Journal of Science. 2023; 2(12), 53–65. https://doi.org/10.14295/bjs.v2i12.422
20. Alamdarloo GH, Mradi H. The effectiveness of sensory integration intervention on the emotional-behavioral problems of children with autism spectrum disorder. Advances in Autism. 2021; 7(2): 152-166. https://doi.org/10.1108/AIA-12-2019-0051
21. Samad A, Aslam FM, Khan H, Tabassum M. Effects of Sensory Integration to Manage Behavior Problems of Children with Autism Spectrum Disorder. Allied Medical Research Journal. 2024; 2 (1): 203-212. https://doi.org/10.59564/amrj/02.01/023
22. Raditha C, Handryastuti S, Pusponegoro HD, Mangunatmadja I. Positive behavioral effect of sensory integration intervention in young children with autism spectrum disorder. Pediatr Res. 2023;93(6):1667-1671. doi:10.1038/s41390-022-02277-4
23. Karim, Amel E. Abdel and Amira. H. Mohammed. Effectiveness of sensory integration program in motor skills in children with autism. Egyptian Journal of Medical Human Genetics. 2015; 16: 375-380.
24. Wang Z, Gui Y, Nie W. Sensory Integration Training and Social Sports Games Integrated Intervention for the Occupational Therapy of Children with Autism [retracted in: Occup Ther Int. 2023 Aug 16;2023:9823565. doi: 10.1155/2023/9823565]. Occup Ther Int. 2022;2022:9693648. Published 2022 Aug 30. doi:10.1155/2022/9693648
25. Leong HM, Carter M, Stephenson J. Systematic review of sensory integration therapy for individuals with disabilities: Single case design studies. Res Dev Disabil. 2015;47:334-351. doi:10.1016/j.ridd.2015.09.022
26.Randell E, Wright M, Milosevic S, et al. Sensory integration therapy for children with autism and sensory processing difficulties: the SenITA RCT. Health Technol Assess. 2022; 26(29):1-140. doi:10.3310/TQGE0020
27. McElhanon BO, McCracken C, Karpen S, Sharp WG. Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. Pediatrics. 2014;133(5):872-883. doi:10.1542/peds.2013-3995
28. Mazurek MO, Vasa RA, Kalb LG, Kanne SM, Rosenberg D, Keefer A, Murray DS, Freedman B, Lowery LA. Anxiety, sensory over-responsivity, and gastrointestinal problems in

children with autism spectrum disorders. J Abnorm Child Psychol. 2013 Jan;41(1):165-76. doi: 10.1007/s10802-012-9668-x.
29. Finegold SM, Summanen PH, Downes J, Corbett K, Komoriya T. Detection of Clostridium perfringens toxin genes in the gut microbiota of autistic children. Anaerobe. 2017;45:133-137. doi:10.1016/j.anaerobe.2017.02.008
30. Doenyas C. Dietary interventions for autism spectrum disorder: New perspectives from the gut-brain axis. Physiol Behav. 2018;194:577-582. doi:10.1016/j.physbeh.2018.07.014
31. Pulikkan J, Mazumder A, Grace T. Role of the Gut Microbiome in Autism Spectrum Disorders. Adv Exp Med Biol. 2019;1118:253-269. doi:10.1007/978-3-030-05542-4_13
32. Ghalichi F, Ghaemmaghami J, Malek A, Ostadrahimi A. Effect of gluten free diet on gastrointestinal and behavioral indices for children with autism spectrum disorders: a randomized clinical trial. World J Pediatr. 2016;12(4):436-442. doi:10.1007/s12519-016-0040-z
33. Rose DR, Yang H, Serena G, et al. Differential immune responses and microbiota profiles in children with autism spectrum disorders and co-morbid gastrointestinal symptoms. Brain Behav Immun. 2018;70:354-368. doi:10.1016/j.bbi.2018.03.025
34. Grzegrzółka P, Jarzyna R. The impact of gluten ingestion on pathogenesis of neurological disorders. Advances in Hygiene and Experimental Medicine. 2019;73(null):197-216. https://doi.org/10.5604/01.3001.0013.1936.
35. Toh MC, Allen-Vercoe E. The human gut microbiota with reference to autism spectrum disorder: considering the whole as more than a sum of its parts. Microb Ecol Health Dis. 2015;26:26309. Published 2015 Jan 28. doi:10.3402/mehd.v26.26309
36. Piwowarczyk A, Horvath A, Łukasik J, Pisula E, Szajewska H. Gluten- and casein-free diet and autism spectrum disorders in children: a systematic review. Eur J Nutr. 2018;57(2):433-440. doi:10.1007/s00394-017-1483-2
37. Mychasiuk R, Rho JM. Genetic modifications associated with ketogenic diet treatment in the BTBRT+Tf/J mouse model of autism spectrum disorder. Autism Res. 2017;10(3):456-471. doi:10.1002/aur.1682
38. Newell C, Bomhof MR, Reimer RA, Hittel DS, Rho JM, Shearer J. Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder. Mol Autism. 2016;7(1):37. Published 2016 Sep 1. doi:10.1186/s13229-016-0099-3
39. Allan NP, Yamamoto BY, Kunihiro BP, Nunokawa CKL, Rubas NC, Wells RK, Umeda L, Phankitnirundorn K, Torres A, Peres R, et al. Ketogenic Diet Induced Shifts in the Gut

Microbiome Associate with Changes to Inflammatory Cytokines and Brain-Related miRNAs in Children with Autism Spectrum Disorder. Nutrients. 2024; 16(10):1401. https://doi.org/10.3390/nu16101401

40. Napoli E, Dueñas N, Giulivi C. Potential therapeutic use of the ketogenic diet in autism spectrum disorders. Front Pediatr. 2014;2:69. Published 2014 Jun 30. doi:10.3389/fped.2014.00069

41. Wu X, Zhou Y, Xi Y, et al. Polyphenols: Natural Food-Grade Biomolecules for the Treatment of Nervous System Diseases from a Multi-Target Perspective. Pharmaceuticals (Basel). 2024;17(6):775. Published 2024 Jun 13. doi:10.3390/ph17060775

42. Malaguarnera M, Khan H, Cauli O. Resveratrol in Autism Spectrum Disorders: Behavioral and Molecular Effects. Antioxidants (Basel). 2020;9(3):188. Published 2020 Feb 25. doi:10.3390/antiox9030188

43. Gogou M, Kolios G. Are therapeutic diets an emerging additional choice in autism spectrum disorder management?. World J Pediatr. 2018;14(3):215-223. doi:10.1007/s12519-018-0164-4

44. Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour - epigenetic regulation of the gut-brain axis. Genes Brain Behav. 2014;13(1):69-86. doi:10.1111/gbb.12109

45. Ohland CL, Kish L, Bell H, et al. Effects of Lactobacillus helveticus on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. Psychoneuroendocrinology. 2013;38(9):1738-1747. doi:10.1016/j.psyneuen.2013.02.008

46. Gilbert K, Arseneault-Bréard J, Flores Monaco F, et al. Attenuation of post-myocardial infarction depression in rats by n-3 fatty acids or probiotics starting after the onset of reperfusion. Br J Nutr. 2013;109(1):50-56. doi:10.1017/S0007114512003807

47. Pineiro M, Asp NG, Reid G, et al. FAO Technical meeting on prebiotics. J Clin Gastroenterol. 2008;42 Suppl 3 Pt 2:S156-S159. doi:10.1097/MCG.0b013e31817f184e

48. Hsiao EY, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013;155(7):1451-1463. doi:10.1016/j.cell.2013.11.024

49. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring. Cell. 2016;165(7):1762-1775. doi:10.1016/j.cell.2016.06.001

50. Schmitt LM, Smith EG, Pedapati EV, et al. Results of a phase Ib study of SB-121, an investigational probiotic formulation, a randomized controlled trial in participants with autism

spectrum disorder. Sci Rep. 2023;13(1):5192. Published 2023 Mar 30. doi:10.1038/s41598-023-30909-0

51. Mazzone L, Dooling SW, Volpe E, et al. Precision microbial intervention improves social behavior but not autism severity: A pilot double-blind randomized placebo-controlled trial. Cell Host Microbe. 2024;32(1):106-116.e6. doi:10.1016/j.chom.2023.11.021

52. Savignac HM, Corona G, Mills H, et al. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. Neurochem Int. 2013;63(8):756-764. doi:10.1016/j.neuint.2013.10.006

53. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PW. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology (Berl). 2015;232(10):1793-1801. doi:10.1007/s00213-014-3810-0

54. Grimaldi R, Gibson GR, Vulevic J, et al. A prebiotic intervention study in children with autism spectrum disorders (ASDs). Microbiome. 2018;6(1):133. Published 2018 Aug 2. doi:10.1186/s40168-018-0523-3

55. Sbahi H, Di Palma JA. Faecal microbiota transplantation: applications and limitations in treating gastrointestinal disorders. BMJ Open Gastroenterol. 2016;3(1):e000087. Published 2016 May 9. doi:10.1136/bmjgast-2016-000087

56. Zhang J, Zhu G, Wan L, et al. Effect of fecal microbiota transplantation in children with autism spectrum disorder: A systematic review. Front Psychiatry. 2023;14:1123658. Published 2023 Mar 2. doi:10.3389/fpsyt.2023.1123658

57. Alharthi A, Alhazmi S, Alburae N, Bahieldin A. The Human Gut Microbiome as a Potential Factor in Autism Spectrum Disorder. Int J Mol Sci. 2022;23(3):1363. Published 2022 Jan 25. doi:10.3390/ijms23031363

58. D'Argenio V. The Prenatal Microbiome: A New Player for Human Health. High Throughput. 2018;7(4):38. Published 2018 Dec 11. doi:10.3390/ht7040038

59. Kang DW, Adams JB, Gregory AC, et al. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome. 2017;5(1):10. Published 2017 Jan 23. doi:10.1186/s40168-016-0225-7

60. Kang DW, Adams JB, Coleman DM, et al. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Sci Rep. 2019;9(1):5821. Published 2019 Apr 9. doi:10.1038/s41598-019-42183-0

61. Yang Y, Tian J, Yang B. Targeting gut microbiome: A novel and potential therapy for autism. Life Sci. 2018;194:111-119. doi:10.1016/j.lfs.2017.12.027

62.Geschwind DH, State MW. Gene hunting in autism spectrum disorder: on the path to precision medicine. Lancet Neurol. 2015;14(11):1109-1120. doi:10.1016/S1474-4422(15)00044-7

63. Ronemus M, Iossifov I, Levy D, Wigler M. The role of de novo mutations in the genetics of autism spectrum disorders. Nat Rev Genet. 2014;15(2):133-141. doi:10.1038/nrg3585

64. Buxbaum JD. Multiple rare variants in the etiology of autism spectrum disorders. Dialogues Clin Neurosci. 2009;11(1):35-43. doi:10.31887/DCNS.2009.11.1/jdbuxbaum

65.Vorstman JA, Spooren W, Persico AM, et al. Using genetic findings in autism for the development of new pharmaceutical compounds. Psychopharmacology (Berl). 2014;231(6):1063-1078. doi:10.1007/s00213-013-3334-z

66.Gerdts J, Bernier R. The broader autism phenotype and its implications on the etiology and treatment of autism spectrum disorders. Autism Res Treat. 2011;2011:545901. doi:10.1155/2011/545901

67.Zhao X, Leotta A, Kustanovich V, et al. A unified genetic theory for sporadic and inherited autism. Proc Natl Acad Sci U S A. 2007;104(31):12831-12836. doi:10.1073/pnas.0705803104

68. Antaki D, Guevara J, Maihofer AX, et al. A phenotypic spectrum of autism is attributable to the combined effects of rare variants, polygenic risk and sex [published correction appears in Nat Genet. 2022 Aug;54(8):1259. doi: 10.1038/s41588-022-01145-5]. Nat Genet. 2022;54(9):1284-1292. doi:10.1038/s41588-022-01064-5

69. Heil KM, Schaaf CP. The genetics of Autism Spectrum Disorders--a guide for clinicians. Curr Psychiatry Rep. 2013;15(1):334. doi:10.1007/s11920-012-0334-3

70.Brown JT, Eum S, Cook EH, Bishop JR. Pharmacogenomics of autism spectrum disorder. Pharmacogenomics. 2017;18(4):403-414. doi:10.2217/pgs-2016-0167

71. Goodson R, Wagner J, Sandritter T, Staggs VS, Soden S, Nadler C. Pharmacogenetic Testing in Patients with Autism Spectrum Disorder Evaluated in a Precision Medicine Clinic. J Dev Behav Pediatr. 2023;44(8):e505-e510. doi:10.1097/DBP.0000000000001215

72. McCracken JT, Badashova KK, Posey DJ, et al. Positive effects of methylphenidate on hyperactivity are moderated by monoaminergic gene variants in children with autism spectrum disorders. Pharmacogenomics J. 2014;14(3):295-302. doi:10.1038/tpj.2013.23

73. Rademacher S, Eickholt BJ. PTEN in Autism and Neurodevelopmental Disorders. Cold Spring Harb Perspect Med. 2019;9(11):a036780. Published 2019 Nov 1. doi:10.1101/cshperspect.a036780

74. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger JI Jr, Hallmayer JF. Autism genetics: opportunities and challenges for clinical translation. Nat Rev Genet. 2017;18(6):362-376. doi:10.1038/nrg.2017.4

75. Forero DA, Vélez-van-Meerbeke A, Deshpande SN, Nicolini H, Perry G. Neuropsychiatric genetics in developing countries: Current challenges. World J Psychiatry. 2014;4(4):69-71. doi:10.5498/wjp.v4.i4.69