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REVIEW

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Cell therapies for autism spectrum disorder: a systematic review of clinical applications

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Abstract

Purpose Autism spectrum disorder (ASD) is a neurodevelopmental condition that affects patients' ability to communicate, engage with others, and behave in certain ways. Despite the existence of several therapy possibilities, an effective treatment for ASD has not yet been identified. Cell therapies have been becoming increasingly recognized in recent years as a potential therapeutic approach for the management of ASD. Different types of cellular products are transplanted using different delivery methods as part of cell therapy, which has the ability to regulate the immune system, demonstrate paracrine, neuro-regenerative, anti-inflammatory, and anti-oxidative stress effects, as well as transfer healthy mitochondria. We have compared the results and findings of completed cell therapy clinical trials for the treatment of ASD in this systematic review.

Methods A total of 547 studies were identified, in which 11 studies were found to be eligible to be included in this review as they were completed cell therapy clinical trials or clinical applications with quantitative results for the treatment of ASD patients.

Results This systematic review provides an overview of clinical trials conducted with different types of cell therapy strategies for the treatment of ASD and their potential mechanisms of action. The limitations and future possibilities for this field of study, as well as the safety and efficacy of cell treatments in ASD, were reviewed.

Conclusion Overall, the evidence suggests that various cell therapy methods may offer a novel and effective treatment option for individuals with ASD, although further research is needed to fully understand the optimal treatment strategy and therapeutic potential.

Keywords Autism spectrum disorder, Cell therapy, Clinical trials, Stem cells

Background

The autism spectrum disorders (ASDs) are a group of various neurodevelopmental illnesses. Although autism itself is the most prevalent ASD, Asperger's syndrome, Rett syndrome (RTT), childhood disintegrate disorders (CDD), and pervasive developmental disorder not otherwise defined (PDD-NOS) are also classified under the category of ASD. It is characterized by deficiencies in social interaction and communication, the existence of restricted interests, and repetitive and stereotypical verbal and nonverbal actions. ASD often manifests in the early stages of life [3, 88]. According to studies, the incidence of ASD is 1.5–1.8% worldwide; however, recent research indicates that the tendency of the number of cases has been rising over the past 10 years [6, 69]. The pathophysiology of ASD is influenced by genetic, environmental, and immunological factors [23, 26, 34, 53, 63, 70, 72, 90]. Up to 1000 potential genes are estimated to be involved in the genetic causes of ASD, which are linked through various inheritance patterns. For instance, synaptogenesis, neurotransmitter metabolism, broadly termed neurometabolic, or healthy mitochondria

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function are among the most important processes and activities that structure the brain [13, 29, 65, 71, 92, 95, 97]. In summary, although the exact etiology of ASD is still unknown due to the complexity of multiple mechanisms involved in the disease, it is suggested that hormonal imbalance, immune dysregulation, chronic neuroinflammation, mitochondrial dysfunction, and oxidative stress conditions caused by certain environmental factors may be inducing ASD in children with genetic predispositions [45].

There is no known cure or proven effective therapy for the condition, despite the progress in early detection and behavioral therapies [24, 25, 84]. Psychotropic drugs, behavioral, occupational, and speech therapy, as well as specific educational and vocational assistance, are all treatment options [22, 27, 59, 66, 87]. Therapeutic strategies that affect immune modulation and regulation of neural connection offer promise in the treatment of these patients since there is evidence of increased neuroinflammation, abnormal neuronal connectivity, and imbalances in the immune system of people with ASD [12]. As paracrine effects (production of cytokines, chemokines, and tissue repair-related growth factors), immunomodulatory properties, and differentiation potential of mesenchymal stem cells (MSCs) are their essential action mechanisms, it is suggested that MSC therapies can show improvements in several neurological conditions in ASD [9, 41, 51, 60, 82–84]. Besides MSCs, various other types of cellular products like mononuclear cells derived from cord blood [51] and/or from bone marrow [61, 77, 78] and fetal stem cells [10] have also been used for the treatment of ASD. There have been no safety issues reported in these trials, which have generally reported benefits in behavior, socializing, speech and language patterns, and brain metabolism. Different studies have used different diagnostic or evaluation tools for ASD which can be listed as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Childhood Autism Rating Scale (CARS), Gilliam Autism Rating Scale (GARS), the Autism Treatment Evaluation Checklist (ATEC), the Vineland Adaptive Behavior Scales (VABS), the Clinical Global Impression Scales for the Severity of Illness (CGI-S) and Global Improvement (CGI-I), Pervasive Developmental Disorder Behavior Inventory (PDDBI), Expressive One-Word Picture Vocabulary Tests (EOWPVT), Receptive One-Word Picture Vocabulary Test (ROWPVT), Indian Scale For Assessment of Autism (ISAA), Functional Independence Measure Scales (FIM and pediatric version Wee-FIM), Stanford Binet Knowledge/fluid reasoning subtests, positron emission tomography–computed tomography (PET-CT), and electroencephalography (EEG) tests. Details of these diagnostic and evaluation tools can be found in Table 1.

The optimum method of delivery, cell source, processing, cell doses, and administration intervals should be determined, as well as whether or not any of these elements have an influence on the treatment's final result. Therefore, using a systematic review of the existing scientific literature, we evaluated the effectiveness and safety of these stem cell therapies as well as their impact on cognitive and behavioral deficits.

Materials and methods

Eligibility criteria

Clinical trials conducted with children and adolescent populations (age 3–18 years) who were diagnosed with ASD, regardless of region, gender, or race were included in this systematic review. Different types of cell therapies on autistic children without placing any restrictions on injection timings, delivery routes, or dosage were examined. Trials in which stem cells were a component of a complicated intervention as well as any prospective controlled clinical investigations of stem cell treatment on autistic individuals were included. Non-human trials, qualitative research, clinical applications without any post-op quantitative results, and studies that did not offer comprehensive results were all excluded.

Literature search and study selection

The literature was searched using 4 databases, including PubMed, U.S. National Library of Medicine (Clinicaltrials.gov), and Embase and Cochrane Library to identify articles published from 2012 to December 2022. Studies were excluded if they were (a) non-human trials, (b) reviews and other studies not designed as clinical trials or clinical applications without adequate quantitative results, or (c) without retrievable full-length articles.

Data collection and quality evaluation

A total of 547 studies (PubMed, *n*=401; ClinicalTrials.org, *n*=46; Embase, *n*=42; Cochrane Library, *n*=58) were identified in the included databases. A total of 11 studies were found to be eligible to be included in this systematic review as they were completed cell therapy clinical trials or clinical applications with quantitative results for the treatment of ASD patients (Fig. 1).

Results

Characteristics of included studies

Eleven studies that were found eligible for analysis were first classified according to the cell type used in the treatment of autism. Three of them have used mononuclear cells (MNCs) derived from the autologous bone marrow, 4 of them were conducted with autologous or allogeneic cord blood, 2 studies were carried out using mesenchymal stem cells (MSCs) derived from bone marrow and umbilical

Table 1 Details of diagnostic and/or evaluation tools used in studies included in this review

Name of the Tool	Use	Explanation
DSM	Diagnostic	The "DSM," a reference work on mental health and brain-related illnesses and problems is written, edited, reviewed, and published by the American Psychiatric Association (APA) [1, 2, 6, 9, 39, 45, 73, 74, 88, 91]. It offers concise, in-depth descriptions of illnesses relating to the brain and mental health. Additionally, it describes and illustrates the symptoms and indicators of such illnesses and identifies the severity level of ASD. The latest edition of this reference book is the 5th edition (DSM-5).
CARS	Diagnostic	The CARS [74] is a 15-item observation-based rating scale that is intended to distinguish autistic children from those who are experiencing developmental delays without showing any signs of autism. The CARS is designed to be utilized by highly skilled raters as part of a broader multi-method approach that also includes behavioral observations, interviews with main caregivers, an evaluation of intellectual functioning, and a thorough developmental and family history [74]. According to a seven-point rating scale (1, 1.5, 2…4), each of the 15 items is classified from "within normal limits for that age," which is coded as one, to "severely abnormal for that age," which is coded as four [75]. The ratings for each of the 15 elements are added up to create a final score. CARS overall scores vary from a low of 15 (all items within normal limits) to a high of 60 (all things highly aberrant). In 2010 Schopler and colleagues published the Second Edition (CARS2) [76].
GARS	Diagnostic	A common diagnostic technique for determining if a person has ASD is the GARS (Gilliam Autism Rating Scale). It was created by James E. Gilliam and is intended to help educators, psychologists, and doctors recognize and diagnose ASD [32]. Three sub-scales make up the 56 items that make up the GARS: Stereotyped Behaviors: This subscale focuses on the stereotyped and repetitive behaviors that are frequently seen in people with ASD. It evaluates the existence and intensity of actions including body swaying, echolalia, and hand flapping. Communication: The individual's verbal and nonverbal communication skills are evaluated by this sub-scale. It evaluates skills in social language, expressive language, and receptive language, among other areas. Social Interaction: This sub-scale focuses at the person's social interaction abilities and any deficiencies brought on by an ASD diagnosis. It evaluates actions pertaining to interpersonal interactions with peers, social responsiveness, and social play. The GARS is seen to be an important diagnostic tool for ASD, especially when used in conjunction with other evaluation tools and clinical judgment. It offers a systematic method for assessing ASD-related behaviors and aids doctors in determining the severity of symptoms across different domains.
VABS	Diagnostic	The VABS is a thorough adaptive behavior assessment that produces composite standard scores in three domains: communication, daily living skills, and socialization [86]. The Adaptive Behavior Composite score (ABC), which combines the three core domain scores, is calculated. Items are rated on a 3-point scale as 0 (never), 1 (sometimes), and 2 (usually) doing a behavior. Items are arranged in a developmental sequence within each subdomain. The Receptive, Expressive, and Written subdomains of the Communication domain evaluate the behaviors required to interact with others vocally and in writing. The Personal, Domestic, and Community subdomains of the Daily Living Skills domain examine the behaviors required to be self-sufficient in personal care, housekeeping, and community functioning. Its latest edition was published in 2016 (VABS-3) [86].
ISAA	Diagnostic	The National Institute for the Empowerment of Persons with Intellectual Disabilities, Government of India, created the ISAA screening tool to aid in the early detection of autism. In order to diagnose autism, the ISAA, an objective assessment instrument for people with autism, employs observation, clinical behavior evaluation, testing via contact with the individual, as well as information from parents or other caregivers. The ISAA comprises of 40 items, each of which is graded on a range of 1 to 5 (always). Six domains—social interaction and reciprocity, emotional response, language and communication, behavior patterns, cognitive component, and sensory aspects—are used to categorize the 40 items that make up the ISAA [14].
ATEC	Measuring changes in severity of ASD in response to a treatment	The ATEC is a questionnaire that caretakers administer to track changes in ASD severity in response to therapy. Four subscale scores are presented along with a total score. The first three subscales' questions are graded on a 0–2 scale. Health/Physical/Behavior, the fourth subscale, is graded on a 0–3 point scale. Speech/Language/Communication, the first subscale, has 14 items with a score range of 0–28. Participants can score between 0 and 40 on the 20 items that make up the Sociability subscale. With 18 items and a score range of 0–36, the third subscale measures sensory and cognitive awareness. Finally, there are 25 items on the Health/Physical/Behavior subscale. The total score, which varies from 0–179 points, is determined by adding the results from each subscale. Lower scores reflect less severe ASD symptoms [68].

Table 1 (continued)

Name of the Tool	Use	Explanation
CGI	Evaluating the severity and improvement of psychiatric diseases	To evaluate the severity and improvement of psychiatric diseases, the rating scales CGI-I (Clinical Global Impressions-Improvement) and CGI-S (Clinical Global Impressions-Severity) are often used in clinical research and treatment. Based on observations and interactions with the patient, they offer a clinician's subjective assessment. The CGI-I is used to determine how much a patient's condition has changed or improved from its initial (pre-treatment) state. The CGI-S is a tool used to evaluate the severity of a disease in a patient at a certain period. It offers a general assessment of the patient's discomfort, functional impairment, and symptom severity. The CGI-S aids physicians in determining the severity of a patient's symptoms by giving a picture of the patient's present clinical condition. These rating scales are frequently employed in clinical trials and academic research projects to evaluate the effectiveness of the therapeutic intervention and to offer a standardized assessment of symptom intensity and improvement [36].
PDDBI	Evaluating the severity and improvement of ASD	ASD and other pervasive developmental disorders are evaluated and measured using the PDDBI, a commonly used assessment instrument. The PDDBI is made up of two primary parts: The PDD Behavior Inventory measures problematic patterns of behavior that are frequently seen in people with pervasive developmental disorders. It contains things that cover a range of topics, including aberrant behavior, social interaction, and communication. The inventory gives details on how frequently, severely, and appropriately these behaviors occur. The PDD Screening Test is a screening instrument used to find people who may be at risk of a pervasive developmental disorder. It consists of items that can only be evaluated in two ways: either they are there or they are not, giving a rapid screening evaluation. From infants to adults, the PDDBI may be used to evaluate people of various ages. Caretakers, parents, or experts who are acquainted with the person's conduct frequently complete it. To compare a person's behavior to that of those who are ordinarily developing or people who have pervasive developmental disorders, the PDDBI offers standardized scores and profiles. It can help in diagnosis, planning treatments, and tracking development over time [75].
EOWPVT	Evaluation of expressive vocabulary level	A standardized assessment instrument called the EOWPVT is used to evaluate people's expressive vocabulary levels. It is frequently used to assess language abilities, particularly expressive language abilities, in clinical, educational, and research settings. In the EOWPVT, candidates are shown a sequence of images and asked to verbally describe the term or concept that each image represents. Various semantic categories are covered by the test, including objects, actions, and properties. The individual's remarks are noted and given an accuracy rating. Raw scores, standard scores, percentile ranks, and age equivalents are just a few of the scores that the EOWPVT offers. These results aid in evaluating a person's expressive vocabulary abilities against those of their classmates and in spotting possible language problems. Individuals of all ages, from infants to adults, are eligible to take the exam. It can be given by qualified experts with standardized testing experience, such as speech-language pathologists, psychologists, or educators [30].
ROWPVT	Evaluation of receptive vocabulary skills	The ROWPVT is a test that measures a test-taker's ability to properly match verbalized words to their matching images, and it may be used to evaluate receptive vocabulary skills in children as well as adults. These terms cover things, behaviors, and/or ideas that people frequently encounter. The EOWPVT is frequently combined with this kind of measurement.

Table 1 (continued)

Name of the Tool	Use	Explanation
FIM	Evaluation of functional abilities	The Functional Independence Measure (FIM) and WeeFIM (Functional Independence Measure for Children) are evaluation instruments for assessing the independence and functional abilities of people with a range of disorders, including Autism Spectrum Disorder (ASD). They offer a systematic assessment of a person's level of functional mobility and independence with regard to ADLs. FIM: The FIM is a popular evaluation instrument for determining an individual's degree of independence in ADL. Self-care, sphincter control, transfers, locomotion, communication, and social cognition are among the six areas represented by its 18 items. Each item is given a rating on a 7-point scale, with 1 being the highest level of support and 7 being the lowest. The FIM offers a thorough assessment of a person's functional condition, which can aid with treatment planning and track advancement over time. Functioning Independence Measure for Children, or WeeFIM: A modified version of the FIM called the WeeFIM was created especially for kids, including those with developmental problems like ASD. It evaluates one's functional capacities in the areas of mobility, cognition, and self-care. The WeeFIM consists of 18 questions that assess a range of independent skills, including problem-solving, eating, dressing, bathing, and transferring. Each item is scored on a 7-point scale, same as the FIM. The WeeFIM helps with treatment planning and goal-setting by providing useful data on a child's functional skills [35, 57].
Stanford Binet Knowledge	Evaluation of intelligence	The Stanford-Binet test is a well-known instrument for measuring intelligence. It may be used to assess cognitive capacities in both adults and children. It is neither intended nor especially developed for the diagnosis or evaluation of ASD. Verbal reasoning, non-verbal reasoning, memory, and mathematical reasoning are all comprehensively assessed by the Stanford-Binet exam. It evaluates abilities like verbal comprehension, visual-spatial processing, and problem-solving. A sequence of exercises and questions make up the exam, which gauges a person's cognitive ability throughout a variety of ages. The Stanford-Binet exam can reveal important details about a person's cognitive profile, but it's important to remember that ASD is a complex neurodevelopmental disease that includes a variety of symptoms and difficulties beyond just cognitive ability.

cord, a combination of MNCs and MSCs derived from cord blood was used in 1 study, and 1 study was conducted with fetal stem cells (FSC). The number of patients enrolled, administration route, and cell dosages in these studies varied among each other. Table 2 describes the cell type strategy, application route, dosage, and number of patients enrolled in these studies.

Outcome of studies

Trials conducted with bone marrow-derived mononuclear cells

Three of the analyzed studies were carried out using autologous bone marrow-derived MNCs (Table 3). The most recent one was conducted by Nguyen Thanh et al. (2021) [61] with 30 patients aged between 3 and 7 who were categorized as severe ASD with an average CARS score of 50 (range 40–55.5).

The instruments DSM-5, CARS, VABS-II, and CGI were utilized to diagnose, ascertain the degree of ASD severity, and evaluate the efficacy of the treatment. Furthermore, positron emission tomography-computed tomography (PET-CT) was used to monitor changes in brain metabolism prior to as well as 12 months after the first stem cell transplantation. It is reported that after BM-MNC transplantation, the severity of ASD decreased remarkably in all patients enrolled in this study. After 18 months of follow-up, CARS scores decreased significantly to an average of 46.5 (range 33.5–53.5), classification of ASD according to DSM-5 reduced, and improvements were observed in various aspects including social interaction, eye contact, expressive language, stereotype behaviors, communication, and socialization. The number of patients categorized as DSM-5 level 3 (requiring very significant support) at 18 months after transplantation decreased from 28 to 18. Additionally, it has been reported that improvements in metabolism were seen in some brain regions, including the parietal lobe, frontal lobe, and anterior cingulate gyrus according to PET-CT scans, where severe hypo-metabolism had been noted prior to BM-MNC transplantation, even though the changes were not statistically significant.

It is reported that none of the patients experienced any major adverse reactions during the treatment process. The treatment process was reported to be safe, with just minor side effects occurring. Only 46 (48%) mild and moderate adverse events with symptoms like discomfort,

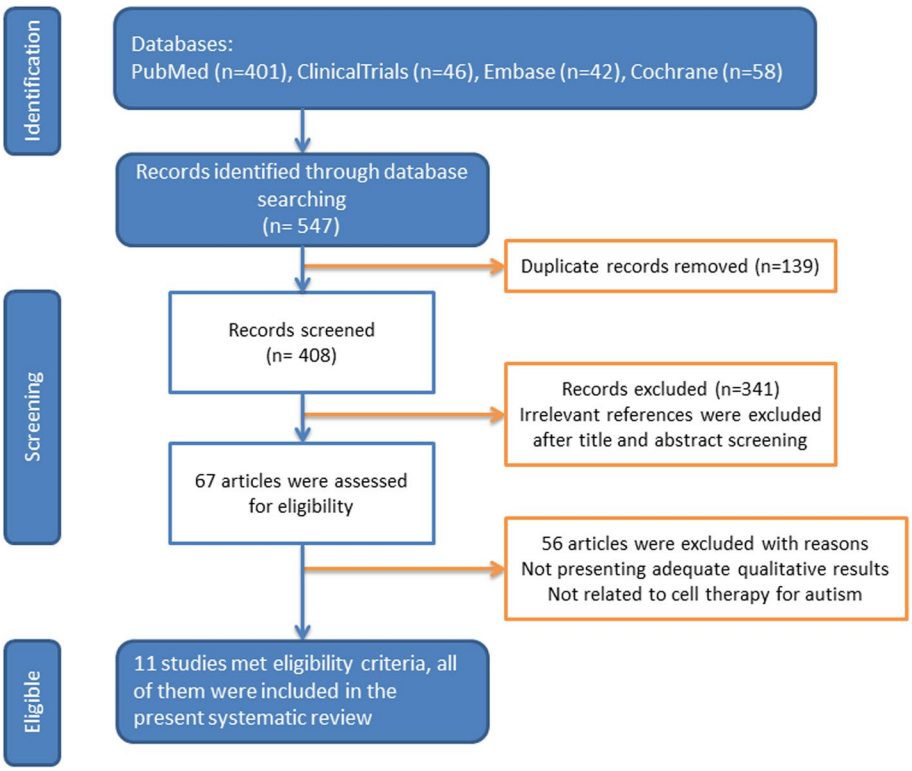

Fig. 1 The inclusion chart of the literature

vomiting, and mild fever were noted. Overall the cellular therapy process was reported to be safe and effective for all patients enrolled.

Another clinical trial carried out with autologous BM-MNCs was conducted by Bansal et al. in 2016 [7] with 10 patients. Although the cell dosage was not mentioned, it is reported that all of the patients improved after intrathecal BM-MNC applications without any adverse effects. Importantly they reported that the maximal efficacy of the treatment was to be within the first year, while the improvement decreased with the increase in the age of patients.

The last study investigated in this systematic review using BM-MNCs for the treatment of ASD was carried out by Sharma et al. [78]. Although further immunophenotype characteristics of the applied cells were not mentioned, the highest cell dosage was used in this study among others using BM-MNCs with an average of 8.19 $\times$ 10^7 cells. CGI, ISAA, FIM, and Wee-FIM scales were utilized as outcome measures to assess the effects of the intervention. Also, PET-CT scanning was introduced before and 6 months after the transplantation in order to monitor functional neuroimaging changes in the brain to assess therapeutic advancements. It was reported that there was a statistically significant difference between the pre- and post-CGI-I scores and ISAA scores only after 1 dose of intrathecal administration of BM-MNCs. Overall, the ISAA score was reduced in 29 out of 32 (90.6%) patients, and on CGI-II scale, 96.9% showed global improvement. Social, emotional, communicational, behavioral, sensory, and cognitive aspects of patients were improved significantly. Another important finding of this study was the proof of increased metabolism after cellular transplantation in areas with hypo-metabolism which was shown by comparative PET-CT scans before and 6 months after cellular transplantation indicating a balancing effect of BM-MNCs. Additionally, it has been reported that 93.8% of patients had no adverse effects and just 6.2% had minor side effects that didn't interfere with function. In addition, the frontal lobe, cerebellum, amygdala, hippocampus, parahippocampus, and mesial temporal lobe were found to have enhanced FDG absorption 6 months after the intervention. Nevertheless, it is important to acknowledge that the average age of the participants involved in this study (10.49) exceeded that of previous investigations, with a subset of patients surpassing 30 years of age.

Trials conducted with cord blood cells

There were 4 trials investigated in this systematic review using autologous and/or allogeneic cord blood cells for the treatment of ASD patients (Table 4).

Table 2 Number of patients, used cell type, administration route, and cell dosage strategies of selected studies

Studies	Patients enrolled		Cell type	Route	Dosage (avg.)	Summary of the outcome
	Treat	Cont				
Bansal et al. [7]	10	-	Auto. BM-MNC	Intrathecal	Not mentioned	Improvement
Sharma et al. [78]	32	-	Auto. BM-MNC	Intrathecal	8.19×10^7	Significant improvement
Nguyen Thanh et al. [61]	30	-	Auto. BM-MNC	Intrathecal	1st: 42.3×10^6/kg MNC (2.6×10^6 CD34 +) 2nd: 40.9×10^6/kg MNC (2.1×10^6 CD34 +)	Significant improvement
Chez et al. [15]	15	15	Auto. CB	Intravenous	16.16×10^6 TNC /kg	No change
Dawson et al. [20]	23	-	Auto. CB	Intravenous	2.6×10^7 TNC /kg	Significant improvement
Dawson et al. [21]	119	61	Auto./Allo. CB	Intravenous	$> 2.5 \times 10^7$ TNC/kg	No change
Simhal et al. [81]	110	55	Auto./Allo. CB	Intravenous	2.5×10^7 TNC /kg	No change
Sharifzadeh et al. [77]	18	18	Auto. BM-MSC	Intrathecal	1st: 0.5—1×10^8 2nd: 0.3—0.5×10^8	No change
Sun et al. [87]	12	-	Allo. UC-MSC	Intravenous	1st: 2×10^6/kg 2nd: 2×10^6/kg 3rd: 2×10^6/kg	Improvement
Lv et al. [51]	23	14	Allo. CB-TNC/Allo. CB-TNC + Allo. UC-MSC	CB-TNC group: 1st IV, 2nd–4th IT Combination group: 1st–2nd IV-IT CB-TNC, 3rd–4th IT UC-MSC	1st: 2×10^6 CB-TNC/kg + 1×10^6 UC-MSC/kg 2nd: 2×10^6 CB-TNC/kg + 1×10^6 UC-MSC/kg 3rd: 2×10^6 CB-TNC/kg + 1×10^6 UC-MSC/kg 4th: 2×10^6 CB-TNC/kg + 1×10^6 UC-MSC/kg	Significant improvement
Bradstreet et al. [10]	45	-	HSC and FSC	Intravenous/subcutaneous	1st: 48×10^6 TNC 2nd: 18.44×10^6 FSC	Significant improvement

Treat treatment group, *Cont* control or placebo group, *Auto* autologous, *Allo* allogeneic, *CB* cord blood, *BM* bone marrow, *UC* umbilical cord, *MNC* mononuclear cell, *MSC* mesenchymal stem cell, *TNC* total nucleated cells, *HSC* hematopoietic stem cell, *IV* intravenous, *IT* intrathecal

Table 3 Summary of the outcome of studies conducted with BM-MNCs

	Sharma et al. [78]	Bansal et al. [7]	Nguyen Thanh et al. [61]
CARS (ISAA)	Improved significantly	Improved	Improved significantly
CGI-I	Improved significantly	-	-
CGI-II	96.9% showed global improvement	-	-
CGI-III	- 21.9% marked therapeutic effect - 40.6% moderate therapeutic - 28% minimal therapeutic effect	-	-
FIM, Wee FIM	No change	-	
VAB-II	-	-	Improved significantly
Social relationship and reciprocity	Improved significantly	-	Improved significantly
Emotional responsiveness	Improved significantly	-	-
Speech, language, communication	Improved significantly	-	Improved significantly
Behavior patterns	Improved significantly	-	Improved significantly
Sensory aspects	Improved significantly	-	Improved significantly
Cognitive component	Improved significantly	-	-
PET-CT	Increased metabolism after cellular transplantation	-	No significant change
Major adverse events	None	None	None

One of the studies was carried out by Dawson et al. (2017) [21] by administering a single dose of autologous umbilical cord blood (AUCB) cells intravenously to 25 children aged between 2 and 5 years who were diagnosed with ASD according to DSM-5. An average of 2.6 $\times 10^7$/kg (range 1–8 $\times 10^7$) total nucleated cells (TNCs) containing 0.3 $\times 10^5$/kg (range 0.1–4.2 $\times 10^5$) CD34+ cells were infused to all patients and followed up for 12 months. No participant experienced any significant adverse events, and only 12 out of 92 AEs (71 mild and 21 moderate) were associated with the infusion, with an allergic response, which was characterized by urticaria and/or cough on the day of the infusion, being the most prevalent. There were no bloodstream, infusion-related, or serious infections in any of the patients. The VABS-II, PDDBI, CGI-S and CGI-I, EOWPVT, and objective eye gaze tracking assessments are only a few of the end measures that showed substantial behavioral changes in this study. This study also revealed a correlation between nonverbal IQ and change, with higher nonverbal IQ being associated to greater behavioral improvements.

Another similar study was conducted by Chez et al. (2018) [15] using AUCB. An average of 16.16 (6.20–31.82) 10^6/kg TNCs were administered intravenously to a total of 30 patients aged between 2 and 7 years old with a diagnosis of ASD based on DSM-4-TR. Fifteen subjects received either an AUCB infusion or a placebo, were assessed at baseline, 12 and 24 weeks later, then had the opposite infusion, and were assessed once again at 12 and 24 weeks later. The average number of TNCs administered was 16.16 (6.20–31.82) $\times 10^6$/kg, and the average percent of viable CD34+ cells was 0.47 ± (0.08–1.48). Patients were followed up for a total of 24 weeks, and there were no serious adverse events nor any allergic reactions experienced and autologous cord blood TNC infusions were reported to be safe according to this study. Three out of 86 minor adverse events experienced were noted to be probably related to the infusion. Outcomes of these studies' results were analyzed according to EOWPVT, ROWPVT, Stanford Binet Knowledge/fluid reasoning subtests and VABS-II. In contrast with Dawson et al.'s study (2017) [21], there was no significant change reported in any of the test results when two groups were compared.

Dawson et al. [20] published their second clinical trial for the treatment of ASD with cord blood cells, but this time by using both autologous and allogeneic cells comparatively also with a placebo group involved in the trial. As a phase 2, prospective, randomized, double-blind study, they have administered a single dose of an average of autologous 26.88 $\times 10^6$ TNC/kg to 56 patients intravenously, a single dose of an average of allogeneic 38.45 $\times 10^6$ TNC/kg to 63 patients (≥4/6 HLA matched) intravenously and 61 patients received placebo. All patients who participated were diagnosed with ASD according to DSM-5 and aged between 2 and 7 years (avg. 5.47±1.65). Clinical outcomes were assessed using VABS-3, PDDBI, CGI-I, CGI-S, EOWPVT tools, and EEG testing at baseline and 6 months after cord blood TNC application. It was reported that no serious adverse events related to the cell therapy were experienced among participants. Primary clinical outcomes of this study showed that there was no significant difference between CB and placebo groups, and also no evidence was reported for any difference between autologous or allogeneic CB applications in terms of VABS-3 scores. The entire cohort showed improvement based on CGI-I, but there was a significant between-group difference in the percentage

Table 4 Summary of the outcome of studies conducted with cord blood TNC

	Chez et al. [15]	Dawson et al. [20]	Dawson et al. [21]	Simhal et al. [81]
CGI-I	No change	Improved significantly	Improved[a]	No change
CGI-S	No change	Improved significantly	No change	-
EOWPVT	No change	Improved significantly	No change	No change
ROWPVT	No change	Improved significantly	-	-
VABS	No change	Improved significantly	Improved	No change
PDDBI	-	-	No change	No change
Daily skills, learning capacity	No change	Improved significantly	-	No change
Social interaction	No change	Improved significantly	No change	No change
Adaptive behavior	No change	Improved significantly	-	No change
Verbal cognitive ability	No change	Improved significantly	-	No change
Brain network reconfiguration	-	-	Significant change[b]	Significant change[b]
Major adverse events	None	None	None	-

[a] CGI rating improvement was observed when only participants with NVIQ≥70 were compared with the placebo group

[b] Significant change was observed when statistical analyses were performed by grouping patients according to their nonverbal IQ

of participants who showed improvement in patients with NVIQ 70 (76.9% in the CB arm versus 57.1% in the placebo arm); it was noted that there was uncertainty in this estimate. Another important finding of this study was observed in EEG results. The subset of subjects with lower NVIQ who got CB, according to the study's findings, showed a substantial decline in beta2 power posterior/social. When participants with NVIQ≥70 were examined separately, the results of this study showed that participants without intellectual disability who received CB showed significantly increased relative alpha $power_{posterior/toys}$ and significantly increased relative beta1 $power_{all\ brain\ regions/social}$ compared with the placebo group.

The last study assessed in this systematic review where cord blood cells were used for the treatment of ASD was a single-site, prospective, randomized, double-blind placebo-control trial conducted by Simhal et al. [81]. The most current study to date on this topic had a placebo group of 61 patients and 180 children between the ages of 2 and 7 who met the DSM-5 criteria for ASD.

One hundred sixty-five children managed to complete 6 months of follow-up. Although further immunophenotype of cells and average cell dosages were not mentioned, it is reported that a minimum TNC dose of 2.5×10^7cells/kg was administered intravenously to the study group of 119 patients, 56 of them with autologous and 63 of them with allogeneic (≥4/6 HLA matched) cord blood units. The number or severity of adverse events experienced in this study cohort was not mentioned. CGI-S and CGI-I scales, EOWPVT tests, VABS-3 interviews, and PDD-BI were used to measure patient's overall level of core autism-related behavior, improvement or worsening of social and communicative behavior, language abilities, adaptive behavior, and autism-related behaviors, respectively. In addition, brain MRI scanning was used to evaluate any changes after cord blood TNC infusions, especially on the white matter connectivity. According to this study, compared to the placebo control group, intravenous cord blood TNC infusion was correlated with decreased streamline connectivity between the dorsolateral prefrontal cortex (dlPFC) and three regions: the inferior frontal gyrus (IFG)—pars opercularis, the caudal middle frontal cortex, and the IFG—pars triangularis in the right hemisphere. It has been found that autistic persons differ in their levels of involvement in each of these brain regions, despite the fact that each of these brain areas is essential for social and communicative functions. These findings imply that cord blood TNC infusion causes reconfiguration in a brain network connected with social and communicative skills, which has previously been linked to the neurobiology of autism. Interestingly, the results varied when statistical analyses were evaluated by grouping participants according to their nonverbal IQ (NVIQ) below or over when collapsing across children with NVIQ<70 and children with NVIQ≥70 when using diffusion-weighted images (DTI) streamlines as the connectivity metric of interest, and it has been reported that there were no regions that distinguished the combined treatment group (allogenic + autologous) from the placebo group. However, the subset of children with NVIQ<70 who received treatment (i.e., the combined allogenic + autologous group), showed less white matter streamlines in the dlPFC to the right IFG—pars triangularis when compared to children who got a placebo infusion. Additionally, in the study population of children with NVIQ≥70 who received allogenic cord blood, they noted diminished white matter streamlines between the left dlPFC and the left IFG—pars opercularis and the left caudal middle frontal cortex in comparison to the placebo group. There were no apparent distinctions in the number of streamlines reported in the subset of children with NVIQ≥70 who either received just autologous cord blood or in the combined allogenic/autologous therapy group. In the combined therapy group (allogenic + autologous), the subset of children with NVIQ≥70 in particular demonstrated a significant improvement in the strength (Ollivier-Ricci curvature, ORC) of the connection between the cuneus and the fusiform gyrus in the left hemisphere. Furthermore, while there were no significant differences in ORC in any of the children with IQ < 70, there was an increase in ORC of the link between the right caudal anterior cingulate cortex (ACC) and the left IFG—pars triangularis in the subset of children who received an infusion of allogenic cord blood at baseline and who also had NVIQ≥70. There was no association observed between the changes in the white matter and the clinical measures evaluated when the changes in either the DTI streamlines or ORC correlated with clinical improvement, including the CGI-I, EOWPVT, VABS-3, and PDD-BI. Also, there was no correlation between improvements on these measures, although a subset of children with NVIQ≥70 showed improvement on CGI-I and the VABS-3, and either change in streamlines or ORC. Overall, Simhal et al.'s [81] findings suggest that DTI can be used to identify distinct patterns of brain connection between children receiving a single infusion of umbilical cord blood and those in the placebo group.

Trials conducted with mesenchymal stem cells

There were 2 studies included in this systematic review which were conducted with MSC administrations for the treatment of ASD (Table 5). The first one was a parallel single-blinded randomized controlled trial carried out by Sharifzadeh et al. (2021) [77] by administering 2 doses (1-month intervals) of autologous bone marrow-derived mesenchymal stem cells (BM-MSCs) intrathecally to 14

patients (4 out of 18 patients abandoned the study) aged between 5 and 15 years, diagnosed with ASD according to DSM-5 criteria. They followed up this study group of 14 patients along with a placebo group of 18 more patients for 1 year. The main outcomes of this study were assessed by CARS, GARS-II, and CGI-I and CGI-S before and after the interventions. Neither short- or long-term adverse events nor allergic reactions in any of the patients were reported in this study during 1-year follow-up. No participants in this trial experienced any short- or long-term adverse effects or allergic responses over the course of the 1-year follow-up. Despite the fact that the results of this study did not show any significant differences between the groups in terms of CARS total score, GARS-II autism index, or CGI global improvement, the improvement in CGI severity of illness was significantly greater in the intervention group compared to the control group during the 12-month study period. Also highlighted by Sharifzadeh and colleagues was that there was only a statistically significant difference between the two groups on the two subscales of the CARS questionnaire, "relationship to people" and "body usage."

The second study with MSCs was conducted by Sun et al. [87] by administering 2×10^6 MSCs/kg intravenously to a total of 12 patients with a median age of 6.4 years (range 4–9 years), by grouping them into 3 cohorts and administering a different number of doses (1, 2, and 3 doses for different groups in 2-month intervals) to each cohort. Assessments for the effectivity of MSC treatment were done according to VABS-3, PDDBI, CGI-S, and CGI-I scales. It is reported that two participants experienced product-related adverse events (one participant experienced hypersensitivity reaction and mild hypotension, and another participant had moderate hypotension; both treatments were completed after administration of IV fluid bolus and an additional dose of methylprednisolone). Also, 66 nonserious AEs and 22 psychiatric or behavioral symptoms were reported which were not related to the MSC product. It is reported that throughout the course of the trial, there were no significant changes in any participant's blood counts, chemistries, basic inflammatory markers (CRP, ESR), humoral and cellular immunological profiles, or signs of graft-vs-host disease. The severity of autism symptoms (PDDBI) with decreases of at least five points indicating improvement, assessments of social communication skills (VABS-3) with increases of three points or more, and expert clinical judgment (CGI-I) ranging from little to significant improvement are some of the measures that have been reported.

Other studies

Another important study on the treatment of ASD with cellular products was carried out by Lv et al. [51]. According to the DSM-4, 23 children with ASD between the ages of 3 and 12 were separated into two groups, with one group receiving just allogeneic CB-TNC therapy (14 patients) and the other receiving both allogeneic CB-TNC and allogeneic UC-MSC therapy (9 patients). The research also included a control group of 14 patients who received just rehabilitative treatment. For 24 weeks, every patient was followed up with. Each study group received 4 doses of cellular products at an interval of 5–7 days. 2×10^6/kg CB-TNC were applied intravenously for the first transplantation in the CB-TNC treatment group and subsequent three transplantations through intrathecal

Table 5 Summary of the outcome of studies conducted with MSCs

	Sharifzadeh et al. [77]	Sun et al. [87]
CARS	No significant difference	-
GARS-II	No significant difference	-
PDDBI	-	Improvement in 5/12
CGI-I	No significant difference	Much improvement in 1/12
CGI-S	Improved significantly	Minimal improvement in 8/12 No improvement in 3/12
Daily skills (VABS)	No significant difference	Improvement in 6/12
Learning skills (PDDBI)	No significant difference	Improvement in 5/12
Relationship to people	Improved significantly	-
Social interaction (VABS)	No significant difference	Improvement in 6/12
Adaptive behavior (VABS)	No significant difference	Improvement in 6/12
Verbal cognitive ability	No significant difference	-
Motor skills (VABS)	No significant difference	Improvement in 6/12
Body usage	Improved significantly	-
Major adverse events	None	2

injections, while the combination group received 2 doses of 2×10^6/kg CB-TNC intravenous and intrathecal infusions each followed by 2 doses of 1×10^6/kg UC-MSC intrathecal injections. Using the CARS, CGI scale, and Aberrant Behavior Checklist (ABC), individuals were assessed for effectiveness at baseline and at 4, 8, 16, and 24 weeks after the first cell transplantation. It was found that no allergic, immunological, or other serious adverse effects occurred in either group receiving a stem cell transplant at the moment of injection or over the full follow-up period. Results were very promising according to almost all assessments followed in this study. At 24 weeks, the combination group's overall CARS scores were significantly lower than those of the CB-TNC and control groups. Also, the CB-TNC group's CARS ratings significantly differed from the baseline at 4 weeks, 8 weeks, and 16 weeks. Although there were no significant variations in CGI scales between the three groups at the baseline, the combination group's CGI-SI levels at 24 weeks were substantially different from those of the control group. In comparison to the control group (7.69%), the frequency of individuals who were better on the basis of the CGI-GI scale rose in the combination group (88.89%) and CBMNC group (50%) after 24 weeks. At 24 weeks, the combination group (88.89%) and CBMNC group (50%) exhibited larger percentages of participants with "marked" and "moderate" effects on the CGI-EI scale when compared to the control group (7.69%). At 24 weeks, there was a statistically significant decline in all groups' ABC scores (combination 59.9%, CBMNC group 38.0%, and control group 17.4%). At 24 weeks following treatment, there were statistically significant changes in "lethargy/social withdrawal," "stereotypic behavior," and overall ABC scores amongst the combination group and the CBMNC and control groups. Interestingly, there was a strong correlation between the ABC and CARS assessment results at each evaluation point and the mean total scores of ABC and CARS at each follow-up point after therapy. Overall, the combination group had generally more robust therapeutic efficacy than the CB-TNC group, according to the study by Lv et al. [51]. It is noted that this may be explained by the action of CB-TNCs and UC-MSCs in synergy, which exerts additional therapeutic effects.

The last study evaluated in this systematic review was conducted by Bradstreet et al. [10] by administering fetal stem cells (FSCs) to 45 children with confirmed autism according to DSM-4-TR with ages ranging from 3 to 15. FSCs were harvested from 5- to 9-week-old human fetuses. Two different cell product approaches were followed with fetal tissues,first, a cell suspension was prepared from hematopoietic stem cells (HSCs) derived from fetal liver, and a second suspension was prepared from fetal brain nervous stem cells. HSCs derived from fetal liver containing a TNC number of $>30\times10^6$/ml with an average of 1.6 ml volume (total of $>48\times10^6$ TNC) were administered to patients on day 1. The TNC suspension was administered via a blood transfusion system along with a 200-ml saline solution. Cultured neuro-progenitor cells derived from fetal brain tissue were administered into the subcutaneous abdominal adipose tissue on day 2. The nucleated neuro progenitor cell dosage of this application was reported to be $>8.70\times10^6$/ml with an average of 2.12 ml total volume ($>18.44\times10^6$ cells for each transplantation). ATEC test and ABC scores were performed for the assessment of the efficiency of the treatment at 6 and 12 months of follow-ups. According to reports of the study, after a year of follow-up, there was a noticeable decrease in the patient's overall ATEC score. Also, the patients' mean scores on the ABC scale showed a substantial decline both after 6 and 12 months. Intriguingly, this study also revealed that the B-lymphocyte (CD19+) count dramatically decreased 6 months after therapy and that CD3+ and CD4+ counts considerably rose 12 months after therapy, suggesting that this may be an indication of better cell-mediated immunity in children. Table 6 summarizes the results of these two studies.

Discussion

Stem cells are essential for organ and tissue regeneration in biological systems. They build organisms that evolve naturally via selection because these cells can self-renew and differentiate into many cell lineages [5, 94]. Cell therapies have recently demonstrated promising results in a number of debilitating, chronic conditions, including spinal cord injuries [19, 47, 48, 80], graft-vs-host disease (GvHD) [8, 46], diabetes and its complications [4, 11, 56], stroke [37, 58], and others, according to clinical data. As may be expected, more researchers are working to determine if cell therapy strategies for the treatment of ASD can be successful.

The primordial finding of this systematic review was that regardless of the type of the cell or the administration route of the cellular product used, none of the patients enrolled in these 11 different trials (a total of 437 patients in treatment groups) experienced any serious adverse effects related to the cell therapy. Considering numerous cell therapy studies on neurological diseases [17, 31, 38, 49, 67, 93] including 11 studies investigated in this systematic review, the safety of cell therapy applications is increasingly supported as studies increase and progress.

The studies that are included in this systematic review give us a glimpse of the areas where future stem cell therapy for autism needs to be standardized. First, cell doses varied in the trials. For studies that used intrathecal

Table 6 Summary of the outcome of other studies conducted with a combination of different cellular products

		Lv et al. [51]		Bradstreet et al. [10]
		CB-TNC group	CB-TNC/UC-MSC Combination group	
CARS		Improved	Improved significantly	-
ATEC		-	-	Improved significantly
CGI-SI		Improved significantly	Improved significantly	-
CGI-EI		Improved significantly	Improved significantly	-
CGI-GI		Improved significantly	Improved significantly	-
ABC	Irritability	No change	No change	Improved significantly
	Lethargy	No change	Improved significantly	
	Stereotypic behavior	Improved significantly	Improved significantly	
	Hyperactivity	No change	No change	
	Inappropriate speech	No change	No change	
	Total score	Improved significantly	Improved significantly	
Major adverse events		None	None	None

BM-MNC applications, the cell dosage ranged from 2.69 to 42.3×10^6/kg BM-MNCs (in Sharma et al.'s 2013 [78] study, the average age at intervention was reported to be 10.4, and the average weight of a 10-year-old child is 30.4 kg according to WHO, so these patients were given an average of 2.69×10^6/kg BM-MNCs). All three BM-MNC studies in this systematic review showed patient improvements in various areas. Even though BM-MNCs may not cure autism, they can reduce severity and improve quality of life without side effects. Its minimal invasiveness, ease of use, and use of autologous cells make it a promising therapeutic option for ASD. In studies using intravenous CB-TNC infusions, the dosage ranged from 16.1 to 26×10^6/kg. Dawson et al.'s [21] study found significant improvements in ASD patients, but their 2020 study, which included a control group and a larger number of patients, found no clinical change. The other two studies [15, 81] using intravenous CB-TNC infusions found no clinical change.

There were two MSC studies with different administration routes. While two doses of $30–100\times10^6$ BM-MSCs were consecutively applied intrathecally in Sharifzadeh et al.'s (2021) [77] study, three doses of 2×10^6/kg UC-MSCs were administered intravenously in Sun et al.'s [87] study. Although some evidence of improvement in about 50% of the patients was reported in Sun et al.'s [87] study, there was not a control group to compare the improvements in this study. Sharifzadeh et al.'s (2021) [77] study found no difference in patients' conditions after MSC therapy when compared to the control group.

Lv et al. [51] found that MSCs and CB-TNCs combined therapy improved effectiveness compared to the control group. CB-TNC. 2×10^6 CB-TNC/kg (i.v. and i.t.), and 1×10^6 UC-MSC/kg (i.t.) were administered to ASD patients. Importantly, this was the only systematic review to show significant improvement in ASD patients after cellular therapy compared to a control group.

In another study [10] where HSCs and FSCs were administered intravenously and subcutaneously consecutively, significant improvement in patients was observed, but there was no control group. 48×10^6 fetal liver-derived TNC (including HSCs) and 18.44×10^6 FSCs derived from fetal brain tissues were used in this study.

The cell type, dosage, and administration route are crucial to cell therapy efficacy. This systematic review found significant improvements in trials with MSCs/MNCs (combined), BM-MNCs, and HSCs/FSCs (combined) in 11 included studies.

Considering hormonal imbalance, immune dysregulation, chronic neuroinflammation, mitochondrial dysfunction, and oxidative stress conditions caused by certain environmental factors may be inducing ASD in children with genetic predispositions [45], cell therapy strategies can be conceived for treatment as it is reported in many studies that certain cellular products (especially MSCs) have anti-inflammation [54, 67], immune system regulation [28, 40], mitochondrial transfer [16, 42], and antioxidative stress properties [1, 100]. Considering improvements in patients reported by intravenous MSC applications performed in Sun et al.'s [87] study and MSC/MNC combined applications performed in Lv. et al.'s [51] study, these potential mechanisms of MSCs may be the reason for clinical improvement in ASD patients. Lv. et al.'s [51] study was especially important

as it reported significant improvement in patients when compared to a control group. In contrast to these studies, Sharifzadeh et al.'s MSC study [77] found no change in CGI severity of illness, but the intervention group improved more than the controls. The administration route distinguished Sharifzadeh et al. [77] from Sun et al. [87]. Systemic anti-inflammation, immune system regulation, mitochondrial transfer, and antioxidative stress effects of MSCs might be achieved better with intravenous administration route. Numerous studies have shown the safety of MSCs [44, 55, 60, 61, 77, 78], but the transplantation pathway was in question. Various tracing methods in animals have demonstrated that MSCs can migrate after an IV injection and may be drawn to the regions that have been damaged [98]. Since the cerebrospinal fluid (CSF) is directly accessible from the intrathecal pathway, its dynamic flow enables cells to easily pass through the spinal cord and brain and reach impaired regions [44, 55, 62, 79, 98, 99]. However, more research is needed to determine if the therapeutically beneficiary effect is obtained by anti-inflammation, immune system regulation, mitochondrial transfer, and antioxidative stress effects of MSCs or the neuro-inflammation reducing and regeneration by the trans-differentiation effect of MSCs or both.

All three intrathecal BM-MNC trials in this systematic review showed patient improvements, especially Nguyen Thanh et al. (2021) [61] and Sharma et al. [78], which had statistically significant results. Despite the lack of control groups, they nonetheless provide evidence that intrathecal BM-MNC infusions in ASD patients are beneficial. BM-MNCs are composed of HSCs, MSCs, and endothelial progenitor cells (EPCs), in addition to lymphocytes, monocytes, and macrophages. Immunomodulatory and neurotrophic cytokines from these cells help the central nervous system regenerate, repair, and replace itself [33, 39, 50, 64, 85, 96]. There are important differences between BM-MNCs and CB-TNCs in the number and variety of stem cell populations. The majority of the stem cells in CB-TNCs are hematopoietic, whereas the stem cells in BM-MNCs include both hematopoietic and MSCs. Another distinction is the age of the cells. The bone marrow of adult donors is the source of BM-MNCs, whereas the umbilical cord blood of a newborn is the source of CB-TNCs. As a result, CB-TNCs may have a higher proliferative capacity and less immunogenicity when compared to BM-MNCs [2, 18, 43, 52]. Since BM-MNCs and CB-TNCs are similar, it is interesting that while BM-MNC studies showed benefits for patients, CB-TNC studies showed no difference between patients and control groups [15, 20, 81]. The main differences between BM-MNC and CB-TNC studies were cell dose and delivery method. The average number of CB-TNCs and BM-MNCs used in studies covered in this systematic review was 23.04×10^6/kg and 55×10^6/kg, respectively. In addition, CB-TNCs were given intravenously in all 4 studies, but BM-MNCs were given intrathecally in all 3. However, Lv et al. [51] found significant improvement with MSC/CB-TNC combination applications via intravenous and intrathecal administrations, suggesting that TNCs enriched with MSCs may be the most effective cellular therapy for ASD patients.

Bradstreet et al.'s [10] study also reported significant improvement in ASD patients after the application of a combination of FSCs and HSCs intravenously and subcutaneously. ATEC and ABC improved significantly despite a comparatively low average cell dosage (48×10^6 TNC and 18.44×10^6 FSC) and no control group. There are studies reporting ASD patients show an increase in the permeability of the blood–brain barrier (BBB) [89]. Given their ability to reestablish appropriate BBB properties, FSCs may also provide a therapeutic target for this endovascular dysfunction [82, 83]. Bradstreet et al.'s achievement may be established by this function of FSCs. There is still a need for improvement in our understanding of how FSCs function in ASDs. To fully describe potential FSC-linked improvements in ASD, larger randomized, placebo-controlled trials, as well as future research investigations are essential.

Conclusion

Regenerative medicine and cellular therapies have lately been investigated for the management of disorders for which there is no effective treatment with traditional therapeutic methods. Since there is currently no treatment for autism, there are limited management alternatives available. In this systematic review, we investigated the effectiveness and safety of several cellular treatments in individuals with ASD. It can be asserted with confidence that there were no serious adverse events reported relating to the application of the cellular products reviewed in this study, regardless of the severity of the condition, application route, or dosage. This demonstrates the safety of cellular treatments and the need to consider them for ASD patients. Given that hormonal imbalance, immune dysregulation, chronic neuroinflammation, mitochondrial dysfunction, oxidative stress conditions, and genetic predisposition are thought to be the causes of ASD, cellular therapies can be thought of as a safe and effective weapon against the condition due to their potential for immune regulation, paracrine effects, neuro-regenerative effects, anti-inflammation, and antioxidative stress properties. The results, however, lack sufficient evidence since they are based on research that did not use a consistent treatment plan. It is crucial to create

a consistent treatment protocol through several trials in order to identify the appropriate cellular therapy type, delivery method, and cell dosage. Post-treatment assessments of cellular therapies also need to be enhanced. These might advance the treatment outcome by leading to the development of cellular therapeutics for autism and its pathogenesis. Stem cell therapy is projected to be used in the clinical treatment of autism and to have significant therapeutic effects; however, there is still more work to be done before this can happen.

Abbreviations

ABC	Aberrant Behavior Checklist
ACC	Anterior cingulate cortex
AE	Adverse event
ASD	Autism spectrum disorder
ATEC	The Autism Treatment Evaluation Checklist
AUCB	Autologous umbilical cord blood
BM	Bone marrow
CARS	Childhood Autism Rating Scale
CB	Cord blood
CD	Cluster of differentiation
CDD	Childhood disintegrate disorders
CGI-I	The Clinical Global Impression Scales for the Global Improvement
CGI-S	The Clinical Global Impression Scales for the Severity of Illness
dlPFC	Dorsolateral prefrontal cortex
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders (5th Edition)
DTI	Diffusion-weighted images
EEG	Electroencephalography
EOWPVT	Expressive One-Word Picture Vocabulary Tests
EPC	Endothelial progenitor cell
FIM	Functional Independence Measure Scales
FSC	Fetal stem cell
GARS	Gilliam Autism Rating Scale
GvHD	Graft vs host disease
HSC	Hematopoietic stem cell
IFG	The inferior frontal gyrus
ISAA	Indian Scale for Assessment of Autism
IT	Intrathecal
IV	Intravenous
MNC	Mononuclear cell
MSC	Mesenchymal stem/stromal cell
NVIQ	Non-verbal IQ
ORC	Ollivier-Ricci curvature
PDDBI	Pervasive developmental disorder behavior inventory
PDD-NOS	Pervasive developmental disorder not otherwise specified
PET-CT	Positron emission tomography–computed tomography
ROWPVT	Receptive One-Word Picture Vocabulary Test
RTT	Rett syndrome
TNC	Total nucleated cells
UC	Umbilical cord
VABS	The Vineland Adaptive Behavior Scales
Wee-FIM	Pediatric Version of Functional Independence Measure Scales

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AA conceived and designed the analysis, collected data, analyzed the results, and drafted the article. EK contributed to the study conception and design and revised the article critically for important intellectual content.

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Declarations

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Consent for publication
Both authors reviewed the results and approved the final version of the manuscript to be published. Both authors hereby give consent for the publication of our personal information in the Middle East Current Psychiatry Journal. This information includes, but is not limited to, our name, age, sex, and any other information that is included in the article. We also understand that we are granting the publisher the exclusive right to publish the article in all languages, in whole or in part. We retain the right to use the article for our own purposes, such as teaching, lecturing, and presenting at conferences.

Competing interests
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