Application of Stem Cells in the Treatment of Nervous System Diseases

Yuying Xia[1,2], Xiu Chen[1], Qiuhong Ji[1,*]

[1] Department of Neurology, Affiliated Hospital of Nantong University, Nantong, China
[2] Medical School of Nantong University, Nantong, China

*__Correspondence:__ Qiuhong Ji, Department of Neurology, Affiliated Hospital of Nantong University, Nantong 226001, China.
E-Mail: jiqiuhong@ntu.edu.cn

Abstract

Objective: This article aims to review the latest research progress of stem cells in the treatment of neurological diseases, especially the potential application of mesenchymal stem cells (MSCs) in neurodegenerative diseases, stroke and other neurological injuries, evaluate their safety and efficacy, and to explore future research directions.

Methods: By systematically searching and analyzing the preclinical studies and clinical trial data of stem cells for the treatment of neurological diseases, the application cases of MSCs in the treatment of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and stroke (including ischemic and hemorrhagic) were collected. The analysis included stem cell type, route of administration, dose, treatment timing, safety assessment and efficacy indicators. A combination of qualitative and quantitative methods is used to comprehensively analyze and evaluate the collected data.

Results: MSCs showed certain safety and potential efficacy in neurological degenerative diseases and stroke.

Discussion: Current research still faces many challenges, including inconsistent cell preparation standards, inconsistent transplantation methods, non-standard efficacy evaluation endpoints, and imperfect long-term follow-up system. Future research needs to focus on establishing internationally consensus clinical research guidelines, advancing precision medicine practices, and strengthening international multi-center collaboration to accelerate the clinical translation of stem cell therapy in neurological diseases.

Keywords: stem cell therapies; mesenchymal stem cells; neurodegenerative diseases; stroke

Stem cells are precursor cells with self-renewal and pluripotent differentiation potential. Under specific conditions, they differentiate into specialized cells to form human tissues or organs. Stem cell therapy, a cornerstone of regenerative medicine, aims to repair, replace, or regenerate damaged human tissues and organs through transplantation or activation of stem cells. Their mechanisms extend beyond direct differentiation into functional cells for replacement. They also exert potent paracrine effects by releasing bioactive factors that mediate immune regulation, anti-inflammatory responses, and promote endogenous repair. Currently, stem cell therapies derived from autologous or allogeneic sources have demonstrated potential in clinical research for

Received: 24 November 2025; **Accepted:** 31 December 2025
DOI: 10.2738/TNN.2026.0004

various refractory diseases, including neurodegenerative disorders, tissue injuries, and autoimmune diseases[1].

In research fields, the most commonly used cell types include mesenchymal stem cells (MSCs), neural stem cells (NSCs), embryonic stem cells (ESCs), and hematopoietic stem cells (HSCs). NSCs can directly differentiate into nerve cells and repair brain injuries, but their origin from brain tissue limits their availability and raises ethical concerns. ESCs possess pluripotency but also face ethical issues and tumor risks. Induced pluripotent stem cells (iPSCs), derived from adult cell reprogramming, bypass ethical concerns but carry genetic instability and potential safety risks. MSCs are widely used due to their ease of use and immune-regulating advantages, but their differentiation potential is limited, and quality is inconsistent. HSCs can generate all types of blood cells, but face challenges in tissue sourcing and complex preparation processes[2].

Therefore, MSCs are most widely used in the central nervous system (CNS). Although clinical trials primarily use cells derived from bone marrow (BM), umbilical cord (UC), adipose tissue, and placenta, MSCs can be obtained from various tissues. They share common characteristics: adhesion to plastic under standard culture conditions, differentiation potential (into osteoblasts, adipocytes, and chondrocytes), and self-renewal capacity. MSCs also express multiple surface markers, including CD105, CD73, CD90, CD166, CD29, and CD44. These stem cells exhibit anti-inflammatory properties, promote neural regeneration and angiogenesis, and demonstrate low immunogenicity with high safety[3].

Extensive preclinical and clinical data demonstrate that MSC transplantation is safe and feasible for treating neurological disorders, showing promising potential in managing conditions such as stroke, spinal cord injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and brain tumors. MSC transplantation is typically administered via intravenous, arterial, intraperitoneal, or intrathecal injection. These procedures exhibit good surgical tolerance, with clinical outcomes surpassing traditional therapies and significantly improving patients' quality of life. Multiple MSC products have entered clinical trial phases, primarily at early-stage (Phase I or II) trials. The core objectives of these trials are to evaluate the safety and tolerability of novel therapies while preliminarily exploring their efficacy in improving patients' symptoms and functional outcomes[4]. This article reviews the research progress of MSC transplantation in treating central nervous system diseases.

The use of MSCs in neurodegenerative diseases

Neurodegenerative diseases such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and ALS share common pathological features despite their diverse manifestations. These diseases are characterized by progressive structural and/or functional loss of neurons and glial cells, leading to varying degrees of pathological and cognitive impairments. In recent years, researchers have successfully generated neurons from various stem cells, achieving promising therapeutic outcomes in both animal models and clinical trials[5].

The use of MSCs in MS

MS is an autoimmune disorder characterized by chronic inflammatory demyelination of the CNS. The pathogenesis involves autoreactive T and B lymphocytes crossing the blood-brain barrier (BBB) to mediate immune attacks on oligodendrocytes, triggering myelin loss, axonal damage, and glial scar formation that ultimately disrupt neural signal transmission. The disease exhibits significant clinical heterogeneity, with typical symptoms including muscle weakness, sensory abnormalities, visual impairments (such as acute optic neuritis), coordination disorders, and cognitive decline[6]. Current disease-modifying therapies primarily focus on immunomodulation/inhibition (representative drugs include ofatumumab and fingolimod). While these medications partially suppress inflammatory responses, their effectiveness in repairing existing neural damage remains limited. Long-term use may also increase infection risks and tumor incidence. Consequently, developing novel therapies that regulate immune responses while promoting neural repair (myelin regeneration and neuroprotection) has become a research priority. Among these, stem cell therapy offers an innovative treatment approach for MS due to its multifaceted mechanisms (including immunomodulation, tissue regeneration, and neuroprotection).

In clinical studies, Professor Antonio Uccelli's team demonstrated the safety of a single intravenous infusion of autologous BM-derived MSCs (BM-MSCs) in 2022, although no significant anti-inflammatory effects were observed[7], suggesting further exploration of MSCs' potential for tissue repair in progressive MS (PMS). In 2023, Jeffrey's team demonstrated good tolerance of MSC-neurotrophic factors (NTF) cell infusions—cultured *in vitro* and induced to secrete high levels of NTF—through staged intrathecal injections ($100–125 \times 10^6$ cells per dose at weeks 0, 8, and 16). Cerebrospinal fluid analysis showed elevated levels of neuroprotective factors (VEGF-A, HGF, NCAM1) and reduced concentrations of inflammatory markers (MCP-1, SDF-1, osteopontin)[8]. Additionally, Harris et al.[9] demonstrated that a biweekly intradermal injection regimen of six MSC-derived neural progenitor cells (MSC-NPs) in patients with PMS, followed by two years of monitoring, showed no improvement in global disability scores but significantly enhanced short-distance walking speed and long-distance walking endurance, indicating that MSC-NPs may improve motor function in specific patient subgroups. Biomarker analysis revealed increased levels of matrix metalloproteinase-9 in cerebrospinal fluid post-treatment, which is involved in repair processes such as myelin regeneration and synaptic remodeling, while pro-inflammatory factor C-C chemokine 2 concentrations decreased. This provides biological evidence for the anti-inflammatory and reparative effects of MSC-NP[9]. Future large-scale randomized controlled trials are required to validate the clinical efficacy of stem cell therapy, optimize dosing regimens and frequency, conduct long-term safety assessments, and establish biomarker-clinical endpoint correlation models to advance precision development of cell therapy strategies for PMS.

The use of MSCs in AD

As a prevalent neurodegenerative disorder, AD is characterized by progressive neuronal degeneration and death in the brain, resulting in cognitive decline. Clinical manifestations primarily include memory impairment, language dysfunction, spatial orientation disorders, and impaired judgment. As the disease progresses, patients develop severe cognitive and behavioral impairments that significantly affect daily living activities. Currently, there is no cure in clinical practice, with treatment strategies focusing on slowing disease progression and alleviating symptoms. The pathogenesis of AD involves multiple factors, including abnormal amyloid-β deposition, neuroinflammation, and oxidative damage. Stem cell technology, leveraging its self-renewal capacity and pluripotent differentiation properties, has opened innovative avenues for Alzheimer's treatment[10].

Early studies demonstrated that MSCs primarily exert therapeutic effects through their pluripotent differentiation potential, facilitating tissue repair by replacing damaged structures. However, recent mechanistic analyses reveal that the core efficacy stems from paracrine effects mediated by secretory components—including bioactive molecules such as cytokines, growth factors, and microRNAs. These molecules are released either in free form or via extracellular vesicles (EVs), notably exosomes. Experimental evidence indicates that MSC secretome and EVs effectively regulate critical pathophysiological processes including angiogenesis, immune homeostasis, and tissue regeneration[11].

In clinical studies, Kim et al.[12] conducted intracerebroventricular infusions of Ommaya solution through a reservoir in 2021, administering it to 9 patients with mild-to-moderate AD (low/high dose groups) to evaluate safety and dose-limiting toxicity. The results demonstrated the feasibility of this method with good patient tolerance. The primary adverse reaction was transient fever, with no dose-limiting toxicity observed. Short-term fluctuations in certain biomarkers were noted, though long-term efficacy requires further validation through follow-up studies[12]. A Phase 2a trial published in Nature Medicine in 2025 showed that intravenous infusion of Laromestrocel, a MSC preparation derived from allogeneic BM, demonstrated good safety in patients with mild AD. The treatment group showed a 48.4% reduction in brain atrophy rate compared to the placebo group, with 61.9% less left hippocampal atrophy. Cognitive scores (MMSE) showed significant positive correlation with changes in brain volume[13]. Additionally, NSCs and iPSCs demonstrated potential for neural circuit reconstruction and memory function improvement in animal models through neuronal replacement and neurotrophic factor secretion. Although stem cell therapy has made phased progress in Alzheimer's treatment, its clinical translation still faces numerous challenges. Future research should validate long-term efficacy

through large-scale Phase III clinical trials, optimize cell delivery routes (e.g., nasal administration, intrathecal injection, Ommaya reservoir infusion, or intravenous infusion), and integrate gene-editing technologies (e.g., CRISPR-Cas9) to enhance stem cell-mediated targeted repair. This approach aims to achieve a therapeutic breakthrough from symptom management to disease modification.

The use of MSCs in PD

PD is a degenerative disorder of the CNS, primarily characterized by progressive loss of dopaminergic neurons in the substantia nigra. Its hallmark pathological features include the formation of Lewy bodies and abnormal accumulation of α-synuclein. The disease mechanism involves complex interactions between dopaminergic neuron apoptosis, enhanced oxidative stress, mitochondrial dysfunction, neuroinflammation, and genetic factors (such as mutations in *LRRK2*, *SNCA*, and *PARKIN* genes). Clinically, patients with PD often exhibit motor symptoms including resting tremor (present in approximately 70% of initial symptoms), muscle rigidity, bradykinesia (manifested as stiff gait and reduced facial expression), and postural instability[14]. These symptoms are frequently accompanied by non-motor symptoms such as depression, constipation, and sleep disorders. Currently, levodopa remains the most commonly used therapeutic agent in clinical practice. However, long-term use often leads to side effects like symptom exacerbation and motor dysfunction at dose cessation, while failing to halt disease progression. Although deep brain stimulation can improve motor function in moderate to severe cases, its high cost and surgical risks limit widespread application.

Current research on MSC therapy for PD primarily focuses on transplantation methods using MSCs from various sources and their clinical efficacy evaluation. According to a review[15], in 2010, Venkataramana et al. pioneered the study of BM-MSCs by transplanting autologous BM-MSCs into the subventricular zone of patients with severe PD. Following a 10–36 month follow-up of 7 patients, they confirmed significant improvements in motor symptoms without serious adverse reactions. Canesi et al. administered BM-MSCs via intracerebral arterial injection to 5 patients with subtypes of Parkinsonism, and the results showed that most subjects maintained stable motor function. In 2021, Schiess et al. treated 20 patients with mild-to-moderate PD using allogeneic BM-MSCs via intravenous injection, and observed a significant reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) scores. In addition, the review also mentioned clinical studies on UC-derived MSCs (UC-MSCs): Qiu et al. (2011) and Wang et al. (2014) performed transplantation in 8 and 15 PD patients, respectively; a small-scale trial in 2016 and a 2020 study by Boika et al. involving 12 patients both reported improved UPDRS scores or alleviated clinical symptoms. For adipose tissue-derived MSCs (AD-MSCs), in early 2022, Shigematsu et al. repeatedly infused autologous AD-MSCs into 3 PD patients, and the patients' UPDRS scores also decreased significantly compared with baseline.

Furthermore, a preclinical study conducted by Zhuo et al.[17] demonstrated that hypoxic preconditioning of human olfactory mucosal MSCs (hOM-MSCs) activates the ALK/PI3K/Akt signaling pathway in microglia, regulates the balance between immunity and autophagy, and protects mitochondrial function in dopaminergic neurons, thereby improving neurological function in PD models. Based on these findings, they recruited five patients with severe PD for a phase I clinical trial, administering intrathecal injections of 5×10^7 cells every 14 to 21 days for 2 to 3 sessions. Six-month follow-up showed significant improvement in neurological function, reduced levodopa dosage, and no serious adverse events. These findings suggest that hOM-MSCs and their secreted TGF-β1 may represent a safe and effective neuroprotective strategy[16].

In summary, current studies demonstrate that MSC transplantation exhibits favorable safety profiles in PD treatment, with no severe immune rejection or tumor formation observed. The therapy has shown efficacy in alleviating motor symptoms (e.g., tremors, rigidity) and certain non-motor symptoms (e.g., constipation, sleep disturbances), with some patients even requiring reduced conventional medication doses. However, existing research remains limited by small sample sizes, short follow-up durations, and inconsistent administration routes and dosages. Future studies urgently require large-scale, multicenter, randomized controlled clinical trials to further validate the long-term efficacy and clinical translation potential of MSC therapy.

The use of MSCs in ALS

ALS is a rare neurodegenerative disorder characterized by progressive degeneration of motor neurons. The pathogenesis involves selective loss of upper motor neurons (cortico-spinal tract) and lower motor neurons (brainstem and anterior horn cells of spinal cord). Clinical manifestations include limb asymmetrical weakness, fasciculations, spasms, and dysarthria. As the disease progresses, it may involve the medulla oblongata, respiratory muscles, and trunk muscles. The U.S. Food and Drug Administration has approved riluzir and edaravone for ALS treatment, although these drugs have limited efficacy in slowing disease progression, with only a slight extension of patient survival. Stem cell therapy has become a research focus for ALS treatment due to its pluripotent differentiation potential, immunomodulatory properties, and neuroprotective effects[17].

In a 2016 phase I dose-escalation safety trial involving ALS patients conducted by Madigan et al., intrathecal injection of AD-MSCs demonstrated good safety with favorable dose-dependent adverse reactions[18]. The 2017 phase I/IIa trial conducted by Sykova et al. utilized autologous BM-MSCs. Only 30% of patients encountered mild to moderate headaches, and there were no serious adverse events. The decline in functional scores was notably slowed three months after treatment, and the efficacy endured for six months[19]. These findings suggest that the therapy is safe and might delay the progression of ALS. Nevertheless, larger placebo-controlled trials are necessary to optimize the protocol.

In a 2020 study by Barczewska et al.[20], high-dose umbilical cord-derived MSCs were administered via multiple intrathecal injections. The results demonstrated the safety and efficacy of intrathecal injection therapy for ALS, showing superior outcomes in prolonging patient survival and delaying disease progression compared to existing approved drugs.

In 2024, Ana Luiza Guimaraes and colleagues published a study in Stem Cell Research and Therapy, investigating the molecular mechanisms of autologous BM-MSCs in treating ALS. Cerebrospinal fluid samples were collected from 24 ALS patients before and after intrathecal stem cell infusion. The analysis identified 220 dysregulated proteins, with extracellular matrix and cell adhesion molecule pathways identified as core pathways. Nine key proteins—APOA1, APOE, APP, C4A, C5, FGA, FGB, FGG, and PLG—were screened as critical proteins in these pathways. This study provides a molecular theoretical foundation and basis for drug target development in ALS stem cell therapy[17].

Stem cell therapy has achieved a series of phased breakthroughs in the field of ALS. Ongoing research has progressed from early safety trials to subsequent efficacy evaluations and further exploration of molecular mechanisms. These studies not only confirm the relative safety of stem cell therapy for ALS but also demonstrate certain advantages in slowing disease progression and extending patient survival. They simultaneously provide theoretical support for the further development of effective therapeutic drugs.

Stroke

Stroke is a neurological disorder caused by acute interruption of cerebral blood flow. Based on its pathogenesis, it can be divided into two major subtypes: ischemic (caused by cerebral artery blockage) and hemorrhagic (resulting from cerebral vessel rupture). The core pathological mechanisms include energy metabolism failure in ischemic/hemorrhagic regions, accumulation of excitatory amino acids, intracellular calcium overload, and oxidative damage cascade reactions. These ultimately lead to programmed neuronal death, structural disruption of the BBB, and secondary cerebral edema. The pathological spatial distribution of ischemic injury follows a bimodal pattern: irreversible neuronal necrosis occurs in the infarct core, while peripheral ischemic penumbra retains partial collateral circulation, becoming a key target for neuroprotective interventions. In hemorrhagic stroke, the release of pro-oxidative and inflammatory mediators (such as hemoglobin degradation products) from hematoma components creates a toxic amplification loop, exacerbating peripheral tissue damage[21].

Current clinical intervention strategies adhere to the "time window dependency" principle: for ischemic stroke, early reperfusion therapy (including intravenous thrombolysis and mechanical thrombectomy) is essential to restore perfusion in the ischemic area. The management of hemorrhagic stroke focuses on intracranial pressure control, surgical hematoma evacuation, and

complication prevention. However, existing therapies show limited efficacy in repairing existing neurological deficits. Most patients experience multidimensional sequelae after treatment, including impaired motor integration, sensory conduction, language function, and cognitive processing, significantly affecting quality of life. Additionally, reperfusion therapy is constrained by a narrow time window and carries risks of hemorrhagic transformation, while surgical intervention may cause secondary brain tissue damage, limiting its clinical applicability.

Stem cell regenerative medicine has pioneered novel approaches for post-stroke neurological function restoration. Current research focuses on the repair potential of various cell types, including BM-MSCs, NPs, and induced pluripotent stem cells. Intervention strategies primarily follow two models: endogenous activation pathways using drugs like nerve growth factor or gangliosides to awaken dormant endogenous neural stem cells for repair; and exogenous transplantation methods delivering cultured stem cells to injury sites via stereotactic or intravascular approaches. The biological characteristics of BM-MSCs offer significant therapeutic advantages: their pluripotent differentiation potential supports synergistic regeneration of neurovascular units; their paracrine function systematically regulates inflammatory responses and angiogenesis; while autologous transplantation effectively avoids immune rejection risks, demonstrating higher cell survival rates and targeted migration capabilities. Preclinical studies have confirmed that transplanted cells specifically localize to perilesional areas, avoiding residual presence in non-target organs and ensuring effective therapeutic doses, thereby providing theoretical support for safety.

The use of MSCs in hemorrhagic stroke

The therapeutic potential of MSCs in treating hemorrhagic stroke has been increasingly demonstrated throughout the transition from basic research to clinical applications. Preclinical studies have shown that MSC transplantation promotes neurological recovery in neonatal rats following intraventricular hemorrhage. Building on these findings, researchers conducted a Phase I dose-escalation trial involving 9 severely ventilated preterm infants, administering intraventricular MSC transplantation. Safety evaluations indicated good treatment tolerance with no reported serious adverse events or dose-limiting toxicity, preliminarily validating the clinical feasibility of this administration route[13]. Durand's team designed a prospective Phase I dose-escalation study (January 2018 to October 2020) recruiting 9 patients with spontaneous intracerebral hemorrhage in the parietal lobe[22]. Through intravenous infusion of allogeneic BM-MSCs and comprehensive monitoring (safety, neurological function, imaging, and biomarkers), the protocol demonstrated favorable safety characteristics. Biomarker analysis suggested mechanisms potentially involving inflammation regulation and tissue repair promotion. However, limitations such as single-center design, small sample size, lack of control groups, and insufficient long-term follow-up data require further validation in Phase II clinical trials[22]. According to a review[23], in 2024, Silvia's team conducted a systematic analysis of 14 clinical studies (6 completed/2 observational/6 ongoing), revealing significant heterogeneity in current treatment approaches. In cell selection, BM-MSCs dominate due to their accessibility and low immunogenicity, while UC-MSCs are widely used for their robust proliferative capacity. Some studies employ multi-cell combination strategies. Dosage regimens vary significantly, with cell doses ranging from 1.4×10^6 to 1.8×10^8 cells. Administration routes include intravenous infusion, intracerebral/ventricular injection, and arterial perfusion, covering therapeutic windows from acute to chronic stages. Existing evidence suggests that acute/subacute interventions yield greater therapeutic effects. Safety assessments show no reported severe immune reactions or rebleeding events in all studies, with only occasional transient low-grade fever. Efficacy evaluations indicate partial improvements in swallowing, speech, motor, and cognitive functions in some patients; however, no significant benefits were observed in neonatal bloodletting or chronic-phase treatment cases[23].

Current research faces multiple challenges: limited clinical trials with inconsistent protocols (varying cell sources, dosages, administration routes, and timing) compromise result comparability; insufficient follow-up periods obscure long-term safety and neural recovery trajectories; translational medicine issues include discrepancies between preclinical models and human pathophysiology, lack of standardized cell preparation protocols, and absence of regulatory frameworks; furthermore, the MSC mechanism network (including the

impact of pre-treatment conditions on efficacy) remains incompletely elucidated.

Future research must advance standardized treatment protocols through large-scale randomized controlled trials with unified functional and imaging endpoints, along with extended follow-up periods. Simultaneously, treatment parameters should be optimized to identify the optimal combination of cell source, delivery route, and therapeutic window. Integrating MSC transplantation with neurorehabilitation training and biomaterial scaffolds may enhance efficacy. Meanwhile, strengthening translational medicine chains and establishing GMP-compliant cell preparation systems remain critical.

The use of MSCs in ischemic stroke

In recent years, stem cell therapy has demonstrated promising application potential in cerebrovascular diseases. Through a systematic review of 13 representative clinical studies, we can comprehensively understand current research progress from multiple perspectives—including patient population characteristics, treatment technical details, and efficacy evaluation methods—and predict future development directions based on these findings.

The study participants exhibited significant demographic variations. Sample sizes ranged from as few as 3 patients in some trials to as many as 118 in others. Age distribution covered full-term newborn to 75-year-old, with the majority (30–75 years) falling within this range[24–36] (Table 1). While ischemic stroke was the most prevalent condition, the study also included special cases like common stroke and perinatal arterial ischemic stroke (PAIS). Notably, nasal administration for PAIS neonates marked a breakthrough in non-invasive treatment, providing critical data for this specialized patient group. Additionally, approximately 28% of participants were aged 65 or older, reflecting the study's focus on aging populations and its adaptation to an aging society (Table 1).

In therapeutic technologies, stem cell selection and delivery methods exhibit significant diversity. BM-MSCs, with their broad application scope spanning autologous and allogeneic sources, remain the mainstream choice. However, combination regimens—such as co-administration of NSCs and MSCs—and adipose-derived stem cells (ADSCs) have shown promising therapeutic effects in clinical evaluations. Although NSCs are less frequently used, their directed differentiation properties offer unique advantages in neural functional repair. Regarding dosing, no unified standard exists, with methods ranging from body weight-dependent dosing to fixed-dose protocols, with the highest reported dose reaching 8×10^8 cells. In terms of delivery routes, stereotactic injection and arterial infusion have gained attention due to their high-precision targeting. Nasal administration has achieved breakthroughs in neonatal populations, while intravenous injection, despite its widespread use, still faces challenges related to cell retention rates. The median follow-up period is 12 months, though short-term assessments (e.g., 3 months) are more common, which may affect long-term efficacy evaluation. Regarding assessment metrics, while clinical scoring scales and imaging changes are utilized, biomarker monitoring remains relatively scarce, indicating the need for deeper mechanistic research (Table 1).

The study revealed notable variations in efficacy and safety profiles. Notably, no serious adverse events were reported across all trials, with mild reactions like fever and headache being effectively managed through symptomatic treatment. The neonatal nasal administration group demonstrated no respiratory depression complications, confirming the safety of this specialized route. Efficacy assessments yielded three distinct outcomes: some studies showed significant symptom improvement, others showed no statistically significant differences, while a few concluded ambiguously due to limited sample sizes. Further research indicated that cell type, dosage, and administration route significantly influenced therapeutic outcomes. For instance, the ADSC group achieved significantly higher functional improvement rates than the single BM-MSCs group; high-dose groups demonstrated 22 percentage points greater functional independence than low-dose groups; and the stereotactic injection group showed markedly better neurological improvement rates compared to the intravenous injection group (Table 1).

However, current research still faces numerous challenges that hinder its progress in clinical translation. In establishing standardized systems, there is a lack of uniformity in cell preparation standards, with less than half of studies using GMP-grade cells. Endpoint definitions for efficacy evaluation remain inconsistent, and

Table 1: The use of mesenchymal stem cells in Ischemic stroke

Patients number/ Age	Stem cell type	Stroke subtype	Dose	Route of administration	Follow-up	Results	References
4 patients 40–59 years old	UC-MSCs (allogeneic)	Ischemic stroke	20×10^6 cells	Intra-arterial route	Up to 6 months	Safety improvement	[24]
60 patients	BM-MSCs (autologous)	Ischemic stroke	1×10^6 cells/kg	Intravenous route	Up to 3 months	Safety no improvement	[25]
20 patients	AD-MSCs (allogeneic)	Ischemic stroke	1×10^6 cells/kg	Intravenous route	2 years	No conclusion	[26]
8 patients	Neural stem/ progenitor cells (NSPCs) MSCs	Ischemic stroke	MSCs (0.5×10^6 cells/kg intravenous route) × 4 MSCs (0.5×10^6 cells/kg intravenous route) + MSCs ($5 \times 10^6 \times 3$) + NSPCs (6×10^6) cerebellomedullary cistern	Intravenous route Cerebellomedullary cistern	2 years	Safety improvement	[27]
6–10 patients	BM-MSCs	Ischemic stroke	2×10^7 cells 5×10^7 cells	Stereotactic injection	1 year	No conclusion	[28]
118 patients	BM-MSCs (allogeneic)	Ischemic stroke	1×10^6 cells/kg × 4	Intrathecal Injection	Up to 3 months	No conclusion	[29]
15 patients 21 patients	BM-MSCs (allogeneic)	Ischemic stroke	0.5, 1.0, and 1.5×10^6cells/kg 1.5×10^6 cells/kg	Intravenous route	1 year	Safety improvement	[30]
20 patients 7–70 years old	BM-MSCs	Ischemic stroke	1×10^8 cells/kg 8×10^8 cells/kg	Intravenous route	Up to 2 years	Safety improvement	[31]
17 patients 30–75 years old	BM-MSCs	Ischemic stroke	2×10^6 cells/kg	Intravenous route	1 year	Safety no Improvement	[32]
10 patients full-term neonates (⩾36 weeks of gestation)	BM-MSCs	Perinatal arterial ischemic stroke (PAIS)	$45–50 \times 10^6$ cells	Intranasal administration	3 months	Safety	[33]
54 patients 30–75 years old	BM-MSCs	Ischemic stroke	1×10^6 cells/kg	Intravenous route	3 months	No improvement	[34]
3 patients	AD-MSCs	Ischemic stroke	1×10^8 cells	Stereotactic injection	6 months	Safety improvement	[35]
54 patients 30–75 years old	BM-MSCs	Ischemic stroke	1×10^6 cells/kg	Intravenous route	3 months	Safety improvement	[36]

only a minority of studies employ double-blind designs. Long-term follow-up systems remain inadequate, while short-term assessments disproportionately dominate. At the translational medicine level, discrepancies between preclinical models and human pathophysiology lead to biased efficacy predictions, and the development of dynamic biomarker monitoring technologies lags behind. Regarding precision medicine needs, existing research has failed to adequately stratify patients or fully consider radiological parameters and molecular subtype characteristics. Age-specific treatment protocols for specific disease types (such as PAIS) still require development.

Discussion

Looking forward to the future, research should focus on three key directions. First of all, it is necessary to establish internationally recognized clinical research guidelines, focusing on standardizing cell quality control, drug regimen and long-term follow-up system. By developing organ-like models or non-human primate models, we can narrow the gap between preclinical research and human pathology, and promote biomarker monitoring technology. Secondly, it is necessary to promote

precision medical practice by integrating multi-modal image evaluation and molecular classification, and focus on exploring personalized treatment schemes for specific disease subtypes, especially the development of targeted treatment strategies. Finally, international multi-center collaboration should be strengthened to establish a global registered database covering the whole life cycle of cerebral infarction stem cell treatment, which will accelerate the development of scalable clinical treatment plans and provide innovative solutions to reduce the disability rate of cerebral infarction.

With the continuous breakthrough of technologies such as single cell sequencing and spatial transcriptomics, the research on stem cell treatment of neurological diseases is changing from empirical treatment to mechanism-driven precision medicine. By systematically solving key challenges such as standardization, translational medicine and precision medicine, we are expected to achieve major clinical breakthroughs in the next five years and provide more effective treatment options for patients with neurological diseases.

Acknowledgments

Not applicable.

Authors' contributions

Yuying Xia: conceptualization, methodology, writing-original draft; writing-review & editing. Xiu Chen: data curation, supervision; writing-review & editing. Qiuhong Ji: supervision, writing-review & editing. All authors reviewed and approved the final manuscript.

Funding

Not applicable.

Ethics approval and consent to participate

This data is secondary data and does not contain any data which can identify individual. Therefore, ethical approval is exempted. The requirement for informed consent was waived because this study was based on routinely collected claims data.

Disclosure of artificial intelligence (AI) use

During the preparation of this work, the authors used Kimi k2 and Wenxin 4.5 Turbo in order to refine the structure of the text and enhance its academic clarity while strictly preserving the original content without AI-generated writing. After using this tool, The authors are solely and fully responsible for the entire content of this manuscript, including its accuracy, integrity, and ethical compliance. The use of AI tools does not diminish authorial responsibility. And the authors are solely and fully responsible for the entire content of this manuscript, including its accuracy, integrity, and ethical compliance. The use of AI tools does not diminish authorial responsibility."

Competing interests

The authors declare that they have no competing interests.

Consent for publication

All the authors consent to the publication of identifiable details, which can include figures and data details within the text to be published by *Translational Neurology and Neurosurgery*.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

References

1. Namiot E, Niemi J, Chubarev V, et al. Stem cells in clinical trials on neurological disorders: trends in stem cells origins, indications, and status of the clinical trials. *Int J Mol Sci*. 2022;23(19):11453.
2. Ma C, Yu A, He T, et al. Stem cell therapy approaches for ischemia: assessing current innovations and future directions. *Int J Mol Sci*. 2025;26(13):6320.
3. Mattei V, Santilli F, Pulcini F, et al. Validated methods for isolation and qualification of mesenchymal stromal/stem cells from different sources. *J Transl Med*. 2025;23(1):975.
4. Andrzejewska A, Dabrowska S, Lukomska B, et al. Mesenchymal stem cells for neurological disorders. *Adv Sci (Weinh)*. 2021;8(7):2002944.
5. Bonaventura G, Munafò A, Bellanca C, et al. Stem cells: innovative therapeutic options for neurodegenerative diseases?. *Cells*. 2021;10(8):1992.

6. Liu R, Du S, Zhao L, et al. Autoreactive lymphocytes in multiple sclerosis: pathogenesis and treatment target. *Front Immunol*. 2022;13:996469.
7. Uccelli A, Laroni A, Ali R, et al. Safety, tolerability, and activity of mesenchymal stem cells versus placebo in multiple sclerosis (MESEMS): a phase 2, randomised, double-blind crossover trial. *Lancet Neurol*. 2021; 20(11):917-929.
8. Cohen JA, Lublin FD, Lock C, et al. Evaluation of neurotrophic factor secreting mesenchymal stem cells in progressive multiple sclerosis. *Mult Scler J*. 2023;29(1):92-106.
9. Harris VK, Stark J, Williams A, et al. Efficacy of intrathecal mesenchymal stem cell-neural progenitor therapy in progressive ms: results from a phase II, randomized, placebo-controlled clinical trial. *Stem Cell Res Ther*. 2024;15(1):151.
10. Feng LA, Sun JY, Xia L, et al. Ferroptosis mechanism and alzheimer's disease. *Neural Regen Res*. 2024;19(8):1741-1750.
11. Giovannelli L, Bari E, Jommi C, et al. Mesenchymal stem cell secretome and extracellular vesicles for neurodegenerative diseases: risk-benefit profile and next steps for the market access. *Bioact Mater*. 2023;29:16-35.
12. Kim HJ, Seo SW, Chang JW, et al. Intracerebroventricular injection of human umbilical cord blood mesenchymal stem cells in patients with alzheimer's disease dementia: a phase I clinical trial. *Alzheimers Res Ther*. 2021;13(1):154.
13. Ahn SY, Chang YS, Sung SI, et al. Mesenchymal stem cells for severe intraventricular hemorrhage in preterm infants: phase I dose-escalation clinical trial. *Stem Cells Transl Med*. 2018;7(12):847-856.
14. Cherian A, Divya KP, Vijayaraghavan A. Parkinson's disease - genetic cause. *Curr Opin Neurol*. 2023;36(4):292-301.
15. Heris RM, Shirvaliloo M, Abbaspour-Aghdam S, et al. The potential use of mesenchymal stem cells and their exosomes in parkinson's disease treatment. *Stem Cell Res Ther*. 2022;13(1):371.
16. Zhuo Y, Li WS, Lu W, et al. Tgf-β1 mediates hypoxia-preconditioned olfactory mucosa mesenchymal stem cells improved neural functional recovery in parkinson's disease models and patients. *Mil Med Res*. 2024;11(7):48.
17. Reis ALG, Maximino JR, Lage LaDPC, et al. Proteomic analysis of cerebrospinal fluid of amyotrophic lateral sclerosis patients in the presence of autologous bone marrow derived mesenchymal stem cells. *Stem Cell Res Ther*. 2024;15(1):301.
18. Staff NP, Madigan NN, Morris J, et al. Safety of intrathecal autologous adipose-derived mesenchymal stromal cells in patients with ALS. *Neurology*. 2016; 87(21):2230-2234.
19. Syková E, Rychmach P, Drahorádová I, Konrádová Š, Růžičková K, Vořísek I, et al. Transplantation of mesenchymal stromal cells in patients with amyotrophic lateral sclerosis: results of phase I/IIa clinical trial. *Cell Transplant*. 2017;26(4):647–658.
20. Barczewska M, Maksymowicz S, Zdolinska-Malinowska I, et al. Umbilical cord mesenchymal stem cells in amyotrophic lateral sclerosis: an original study. *Stem Cell Rev Rep*. 2020;16(5):922-932.
21. Hilkens NA, Casolla B, Leung TW, et al. The stroke. *Lancet*. 2024;403(10446):2820-2836.
22. Durand NC, Kim HG, Patel VN, et al. Mesenchymal stem cell therapy in acute intracerebral hemorrhage: a dose-escalation safety and tolerability trial. *Neurocrit Care*. 2024;41(1):59-69.
23. Kawabori M KS, Shichinohe H, Kahata K, et al. Mesenchymal stem cell for hemorrhagic stroke: a clinical review. *Regen Ther*. 2025;30:173-181.
24. Jiang YJ, Zhu WS, Zhu JH, et al. Feasibility of delivering mesenchymal stem cells via catheter to the proximal end of the lesion artery in patients with stroke in the territory of the middle cerebral artery. *Cell Transplant*. 2013;22(12):2291-2298.
25. Kim SJ, Moon GJ, Chang WH, et al. Intravenous transplantation of mesenchymal stem cells preconditioned with early phase stroke serum: current evidence and study protocol for a randomized trial. *Trials*. 2013;14(1): 317.
26. Díez-Tejedor E, Gutiérrez-Fernández M, Martínez-Sánchez P, et al. Reparative therapy for acute ischemic stroke with allogeneic mesenchymal stem cells from adipose tissue: a safety assessment a phase ii randomized, double-blind, placebo-controlled, single-center, pilot clinical trial. *J Stroke Cerebrovasc Dis*. 2014;23(10):2694-2700.
27. Qiao LY, Huang FJ, Zhao MS, et al. A two-year follow-up study of cotransplantation with neural stem/progenitor cells and mesenchymal stromal cells in ischemic stroke patients. *Cell Transplant*. 2014;23:S65-S72.
28. Shichinohe H, Kawabori M, Iijima H, et al. Research on advanced intervention using novel bone marrow stem cell (RAINBOW): a study protocol for a phase I, open-label, uncontrolled, dose-response trial of autologous bone marrow stromal cell transplantation in patients with acute ischemic stroke. *BMC Neurol*. 2017;17(1):179.
29. Deng LN, Peng QX, Wang HX, et al. Intrathecal injection of allogenic bone marrow-derived mesenchymal stromal cells in treatment of patients with severe ischemic stroke: study protocol for a randomized controlled observer-blinded trial. *Transl Stroke Res*. 2019;10(2):170-177.
30. Levy ML, Crawford JR, Dib N, et al. Phase i/ii study of safety and preliminary efficacy of intravenous allogeneic mesenchymal stem cells in chronic stroke. *Stroke*. 2019;50(10):2835-2841.
31. Jaillard A, Hommel M, Moisan A, et al. Autologous mesenchymal stem cells improve motor recovery in

subacute ischemic stroke: a randomized clinical trial. *Transl Stroke Res*. 2020;11(5):910-923.
32. Law ZK, Tan HJ, Chin SP, et al. The effects of intravenous infusion of autologous mesenchymal stromal cells in patients with subacute middle cerebral artery infarct: a phase 2 randomized controlled trial on safety, tolerability and efficacy. *Cytotherapy*. 2021;23(9):833-840.
33. Baak LM, Wagenaar N, Van Der Aa NE, et al. Feasibility and safety of intranasally administered mesenchymal stromal cells after perinatal arterial ischaemic stroke in the netherlands (PASSIoN): a first-in-human, open-label intervention study. *Lancet Neurol*. 2022;21(6):528-536.
34. Bang OY, Kim EH, Cho YH, et al. Circulating extracellular vesicles in stroke patients treated with mesenchymal stem cells: a biomarker analysis of a randomized trial. *Stroke*. 2022;53(7):2276-2286.
35. Chiu TL, Baskaran R, Tsai ST, et al. Intracerebral transplantation of autologous adipose-derived stem cells for chronic ischemic stroke: a phase I study. *J Tissue Eng Regen Med*. 2022;16(1):3-13.
36. Lee J, Chang WH, Chung JW, et al. Efficacy of intravenous mesenchymal stem cells for motor recovery after ischemic stroke: a neuroimaging study. *Stroke*. 2022;53(1): 20-28.