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Review Article

Application of Stem Cell Therapy in Neurological Disorders: A Systematic Review

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ABSTRACT

Background: Stem cell–based therapy has emerged as a promising regenerative and immunomodulatory approach for neurological disorders, but clinical efficacy remains uncertain because trials differ in disease condition, cell type, delivery route, comparator, and outcome selection. Objective: This systematic review evaluated recent clinical evidence on the safety and efficacy of stem cell–based therapies in adults with neurological disorders. Methods: A structured search of Google Scholar, PEDro, PubMed, TRIP, and MEDLINE was conducted in February 2024 and updated in August 2024. English-language human clinical studies published from 2019 to 2024 were screened. Eligible studies included adults with neurological disorders who received stem cell–based or cell-associated therapy and reported neurological, survival, disability, quality-of-life, biomarker, or safety outcomes. Methodological quality was assessed using trial appraisal domains from PEDro, the JBI checklist, and Cochrane RoB 2. Results: Five studies involving 540 participants were included. Conditions studied were glioblastoma, ischemic stroke, amyotrophic lateral sclerosis, multiple sclerosis, and primary central nervous system lymphoma. Interventions were generally reported as tolerable. Efficacy was heterogeneous: glioblastoma showed a 2.2-month progression-free survival benefit, PCNSL showed higher two-year progression-free survival with myeloablative consolidation, ALS and MS showed subgroup-level benefits, while ischemic stroke showed no clear superiority over placebo. Conclusion: Stem cell–based therapies appear tolerable in selected neurological trials, but efficacy remains inconsistent, condition-specific, and often subgroup-dependent. Larger standardized trials with long-term follow-up are required. Keywords: Stem Cell Therapy; Neurological Disorders; Cellular Therapy; Regenerative Medicine; Rehabilitation; Systematic Review.

INTRODUCTION

Stem cell therapy has emerged as an important area of regenerative medicine because of its potential to repair, replace, or modulate damaged tissues through cellular differentiation, trophic signaling, and immunoregulatory mechanisms. Stem cells are undifferentiated cells capable of self-renewal and differentiation into specialized cell lineages, and they may be derived from multiple sources, including adult tissues, embryonic tissues, and induced pluripotent stem cells (1). Advances in stem cell biology have expanded the therapeutic relevance of these cells beyond traditional hematological applications and have encouraged investigation into their role in complex, chronic, and degenerative diseases (2). Hematopoietic stem cell transplantation is already established in several blood-related disorders, including leukemia, lymphoma, and primary immune deficiencies, where it is used to restore hematopoietic and immune function after intensive treatment or marrow failure (3, 4).

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Neurological disorders represent a major therapeutic challenge because many diseases of the brain, spinal cord, and peripheral nervous system are characterized by progressive neuronal injury, limited endogenous repair, chronic inflammation, and incomplete recovery despite standard medical and rehabilitative care. Conditions such as multiple sclerosis, amyotrophic lateral sclerosis, ischemic stroke, spinal cord injury, glioblastoma, and primary central nervous system lymphoma differ in pathophysiology and prognosis, but all may involve mechanisms that could theoretically be influenced by cell-based therapies, including neuroprotection, immune modulation, tissue repair, and support of neural plasticity (5, 6). Recent literature suggests that stem cell–based approaches may have therapeutic potential in selected neurological conditions, particularly where conventional treatment offers limited restoration of neurological function or disease stabilization (7).

The biological rationale for stem cell therapy in neurological disorders is based on several complementary mechanisms. Stem cells may contribute to neural repair by differentiating into neural-lineage cells, including neurons, astrocytes, and oligodendrocytes, thereby supporting restoration of damaged neural circuits and glial function (8). In addition to direct cellular replacement, stem cells can secrete trophic factors that promote cell survival, angiogenesis, neurovascular support, tissue remodeling, and synaptic plasticity (9, 10). Their immunomodulatory effects may also reduce inflammatory injury within the central nervous system, which is particularly relevant in disorders such as multiple sclerosis, spinal cord injury, and other neuroinflammatory or neurodegenerative conditions (11). These mechanisms provide a plausible basis for clinical investigation; however, the therapeutic effect may vary according to disease type, disease stage, stem cell source, administration route, dose, timing of intervention, and patient selection.

Despite these promising mechanisms, the clinical application of stem cell therapy in neurological disorders remains uncertain. Important concerns include inconsistent efficacy across trials, heterogeneity in cell type and delivery route, limited long-term safety data, risk of immune rejection, tumorigenic potential, ethical issues related to cell sources, and regulatory challenges in translating experimental protocols into routine care (12). In addition, available clinical trials often assess different outcomes, including neurological function, survival, disability progression, progression-free survival, motor performance, quality of life, and safety endpoints, making direct comparison difficult. Therefore, a focused synthesis of recent clinical evidence is needed to clarify whether stem cell–based interventions are safe and whether their efficacy is consistent, condition-specific, or limited to selected patient subgroups.

This systematic review was conducted to evaluate the application of stem cell–based therapy in adult patients with neurological disorders. Using a PICO framework, the population comprised adults with neurological disorders, the intervention was stem cell–based therapy or cellular rehabilitation, the comparator included placebo, standard care, or alternative therapeutic approaches, and the outcomes included neurological function, disease progression, survival-related outcomes, disability, quality of life, and safety. The review aimed to answer the following research question: What is the available clinical evidence regarding the safety and efficacy of stem cell–based therapy in adults with neurological disorders?

MATERIAL AND METHODS

This systematic review was designed to evaluate clinical evidence on the safety and efficacy of stem cell–based interventions in adults with neurological disorders. The review question was structured according to the PICO framework. The population included adult patients diagnosed with neurological disorders, including but not limited to amyotrophic lateral sclerosis, multiple sclerosis, ischemic stroke, glioblastoma, spinal cord injury, and primary central nervous system lymphoma. The intervention was any stem cell–based therapy, including stem cell treatment, stem cell rehabilitation, cellular therapy, regenerative medicine approaches, or related cell-based interventions. Comparators included placebo,

standard care, non-stem-cell treatment, or other rehabilitation or medical approaches, depending on the design of the included trial. Outcomes of interest included neurological function, motor function, disability, disease progression, survival-related outcomes, progression-free survival, quality of life, treatment response, biomarker response, and adverse events.

A structured literature search was conducted in Google Scholar, PEDro, PubMed, TRIP, and MEDLINE. The initial search was performed in February 2024 and updated in August 2024 to identify recent eligible studies. The search was restricted to English-language human studies published between 2019 and 2024. Search terms were developed from the main PICO concepts and included combinations of terms related to stem cell therapy and neurological disorders. The main search string used was: "Stem Cell Therapy" OR "Stem Cell Rehabilitation" OR "Stem Cell" OR "Cell Therapy" OR "Cellular Rehabilitation" combined with "Neurological Disorder" OR "Neurodegenerative Disease." Boolean operators "AND" and "OR" were applied to combine intervention-related and disease-related terms. In PubMed, the search was further focused using the terms "Stem Cell Therapy," "Rehabilitation," and "Neurological Disorder" with the AND operator. Reference lists and eligible citations identified through Google Scholar were also screened to locate additional relevant studies.

Studies were eligible for inclusion if they were original full-text clinical trials published in peer-reviewed journals, written in English, conducted in human participants aged 18 years or older, published from 2019 to 2024, and focused on the safety or efficacy of stem cell–based therapy in neurological disorders. Studies were required to include a clearly defined neurological condition, a stem cell–based intervention, a comparator or control condition where applicable, and clinically relevant outcomes related to neurological function, disease progression, survival, disability, quality of life, or safety. Reviews, case reports, case series, quasi-experimental studies, animal studies, studies involving participants younger than 18 years, non-English articles, studies published outside the selected date range, and studies in which stem cell therapy was not directly evaluated for a neurological condition were excluded.

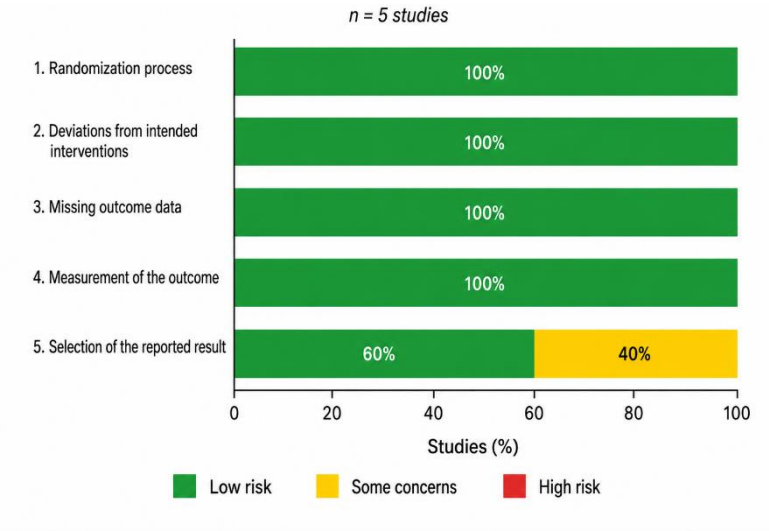

Figure 1 Risk of Bias Chart

All identified records were exported into EndNote for organization and duplicate removal. After removal of duplicates, titles and abstracts were screened against the eligibility criteria. Full-text articles were retrieved for studies that appeared potentially eligible or where eligibility could not be determined from the title and abstract alone. Two reviewers independently screened the records and assessed full-text eligibility. Disagreements were resolved through discussion and verification against the predefined

eligibility criteria. The final included studies were selected only when they met the review objective and provided sufficient methodological and outcome information for qualitative synthesis.

Data extraction was performed independently by two reviewers using a standardized extraction format. Extracted data included author name, publication year, country, study design, sample size, participant age, neurological condition, intervention type, stem cell source, route of administration, comparator, dose where reported, follow-up duration where available, outcome measures, main efficacy findings, and safety findings. After extraction, the data were cross-checked to identify errors, missing fields, and inconsistencies. Because the included studies evaluated different neurological conditions, interventions, administration routes, comparators, and outcome measures, the review used descriptive and qualitative synthesis rather than meta-analysis. Findings were summarized according to study characteristics, methodological quality, safety outcomes, and efficacy outcomes by neurological condition.

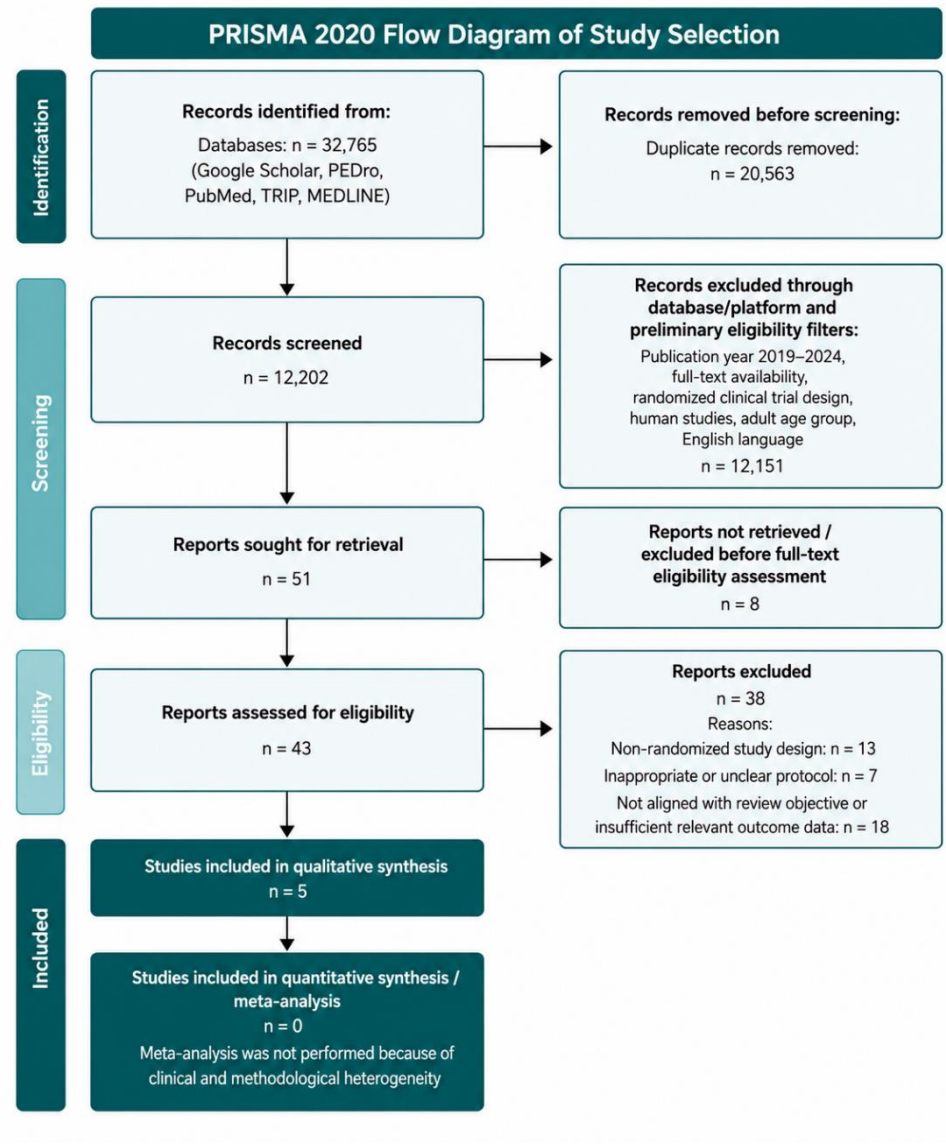

Figure 2 PRISMA Flowchart

Methodological quality and risk of bias were assessed using clinical-trial appraisal domains relevant to randomization, allocation concealment, blinding, incomplete outcome data, selective reporting, and appropriateness of statistical analysis. The PEDro scale was considered for trial-quality appraisal because of its relevance to randomized clinical trials and rehabilitation-related research (13). The Joanna Briggs Institute critical appraisal checklist for randomized controlled trials was used to evaluate methodological quality, including randomization procedures, allocation concealment, baseline comparability, blinding, outcome measurement, follow-up completeness, and statistical analysis (14).

The Cochrane Risk of Bias 2 tool was used to assess potential bias across domains including the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results (15). Risk-of-bias judgments were summarized narratively and visually where applicable.

Data synthesis was conducted without statistical pooling because of clinical and methodological heterogeneity across the included studies. The interventions differed in stem cell type, source, route of delivery, disease target, comparator, and outcome timing, while the included neurological disorders had distinct pathophysiological profiles and endpoint structures. Therefore, outcomes were interpreted within each disease context rather than as a single pooled effect across all neurological disorders. Efficacy findings were distinguished according to whether they represented primary endpoints, secondary endpoints, subgroup findings, or safety observations. Safety outcomes were summarized across studies, with attention to tolerability, adverse events, and treatment-related concerns.

Ethical approval was not required for this systematic review because it used previously published clinical studies and did not involve direct recruitment of human participants or access to identifiable patient data. To support transparency and reproducibility, the review used predefined eligibility criteria, duplicate screening, independent data extraction, structured quality appraisal, and cross-checking of extracted information before synthesis. Data used in the review were derived from published sources, and the extracted dataset is available from the corresponding author on reasonable request.

RESULTS

The database search and screening process identified five clinical studies that met the eligibility criteria for qualitative synthesis. The included studies evaluated stem cell–based or cell-associated therapeutic approaches across five neurological conditions: glioblastoma, ischemic stroke, amyotrophic lateral sclerosis, multiple sclerosis, and primary central nervous system lymphoma. Because the studies differed substantially in disease condition, intervention type, delivery route, comparator, and outcome structure, statistical pooling was not performed. The findings are therefore presented descriptively according to study characteristics, methodological quality, and clinical outcomes.

Table 1. Characteristics of Included Clinical Studies

Author	Country	Sample Size	Age	Neurological Condition	Intervention	Route of Administration	Comparator
Wen	United States	124	≥18 years	Glioblastoma	Autologous dendritic cells pulsed with immunogenic antigens	Intradermal axillary injection	Placebo
Houkin	Japan	206	≥20 years	Cerebral cortical ischemic stroke	HLCM051 / MultiStem	Intravenous	Placebo
Berry	United States	48	18–75 years	Amyotrophic lateral sclerosis	NurOwn MSC-NTF cells	Intramuscular and intrathecal	Placebo
Harris	United States	54	18–65 years	Multiple sclerosis	Autologous mesenchymal stem cell-derived neural progenitor cells	Intrathecal	Saline
Batchelor	United States	108	18–75 years	Primary central nervous system lymphoma	Myeloablative consolidation	Systemic consolidation approach	Nonmyeloablative consolidation

The included studies collectively enrolled 540 participants, with individual study sample sizes ranging from 48 to 206 participants. The largest study was conducted by Houkin in patients with cerebral cortical ischemic stroke, whereas the smallest study was conducted by Berry in patients with amyotrophic lateral sclerosis. Routes of delivery varied across trials and included intradermal, intravenous, intramuscular, and intrathecal administration, reflecting substantial clinical and methodological heterogeneity. The interventions also differed by therapeutic class, including mesenchymal stromal or progenitor cell–based approaches, dendritic cell immunotherapy, MultiStem therapy, and consolidation therapy in primary central nervous system lymphoma.

Table 2. Methodological Quality Domains of Included Studies

Author	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Reporting
Wen	Yes	Yes	Yes	Yes	No	Yes
Houkin	Yes	Yes	Yes	Yes	No	Yes

Author	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Reporting
Berry	Yes	Yes	Yes	Yes	No	Yes
Batchelor	Yes	Yes	Yes	Yes	No	Yes
Harris	Yes	Yes	Yes	Yes	No	Yes

All five included studies reported random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and reporting of prespecified outcomes. Incomplete outcome data were marked as "No" across all studies in the extracted appraisal table. Because the supplied table does not define whether "No" indicates absence of incomplete outcome data or inadequate handling of incomplete outcome data, this domain should be clarified before final submission. Based on the extracted Cochrane RoB 2 summary, the randomization process, deviations from intended interventions, missing outcome data, and outcome measurement domains were reported as low risk across all included studies, while 40% of studies showed some concern in the selection of reported results.

Table 3. Summary of Efficacy Outcomes Across Included Studies

Author	Neurological Condition	Primary Reported Outcome Area	Main Numerical Finding	p-value
Wen	Glioblastoma	Progression-free survival	2.2-month increase	0.011
Wen	Glioblastoma	Overall survival	2.0-month difference	NR
Houkin	Ischemic stroke	Excellent outcome at day 90	Similar proportions	NR
Berry	Amyotrophic lateral sclerosis	ALSFRS-R slope responder analysis	Higher responder proportion	<0.05
Berry	Amyotrophic lateral sclerosis	Early disease progression in rapid progressors	Improved early progression rate	<0.05
Harris	Multiple sclerosis	Timed 25-foot walk and 6-minute walk in EDSS 6.0–6.5 subgroup	Superior performance	NR
Harris	Multiple sclerosis	Cerebrospinal fluid biomarkers, grey matter atrophy, bladder function	Favorable changes	NR
Batchelor	Primary central nervous system lymphoma	Two-year progression-free survival	73% vs 51%	0.02
Batchelor	Primary central nervous system lymphoma	Two-year progression-free survival after consolidation therapy	86% vs 71%	0.21

The efficacy findings were heterogeneous and condition-specific. In glioblastoma, Wen reported a 2.2-month improvement in progression-free survival with ICT-107 compared with placebo, with a statistically significant p-value of 0.011, while the 2.0-month difference in overall survival favored ICT-107 but was not reported as statistically significant in the supplied manuscript. In ischemic stroke, Houkin found similar proportions of excellent outcomes at day 90 between the MultiStem and placebo groups, indicating no clear clinical advantage in the reported primary outcome. In amyotrophic lateral sclerosis, Berry reported statistically significant early improvement in disease progression and ALSFRS-R slope responder outcomes among predefined rapid progressors, although the benefit was subgroup-specific. In multiple sclerosis, Harris reported superior walking performance and favorable biomarker and structural outcomes in patients with greater baseline disability, particularly those with EDSS scores of 6.0–6.5. In primary central nervous system lymphoma, Batchelor reported higher estimated two-year progression-free survival in the myeloablative arm than in the nonmyeloablative arm, with values of 73% and 51%, respectively, and a p-value of 0.02. However, the secondary comparison after consolidation therapy showed 86% versus 71% two-year progression-free survival with a p-value of 0.21.

Table 4. Safety and Overall Clinical Interpretation of Included Studies

Author	Neurological Condition	Safety Finding	Efficacy Pattern
Wen	Glioblastoma	Tolerable	Secondary endpoint benefit
Houkin	Ischemic stroke	Tolerable	No clear superiority
Berry	Amyotrophic lateral sclerosis	Tolerable	Subgroup benefit
Harris	Multiple sclerosis	Tolerable	Subgroup benefit
Batchelor	Primary central nervous system lymphoma	Tolerable	Condition-specific benefit

Across the included studies, stem cell–based or cell-associated interventions were generally reported as tolerable. However, evidence of efficacy was inconsistent. The clearest numerical treatment advantages were observed in progression-free survival among patients with glioblastoma, two-year progression-free survival among patients with primary central nervous system lymphoma, and selected subgroup

outcomes in amyotrophic lateral sclerosis and multiple sclerosis. In contrast, MultiStem therapy for ischemic stroke did not demonstrate clear superiority over placebo in the reported day-90 clinical outcome. Overall, the findings suggest that potential clinical benefit may depend on disease type, patient subgroup, intervention type, delivery route, and outcome selection.

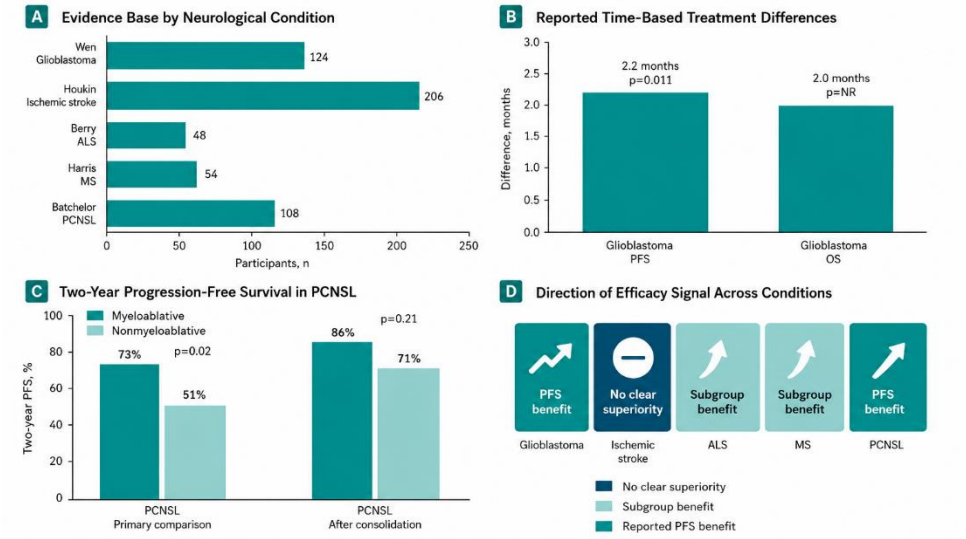

Figure 3 Clinical evidence signals for stem cell–based therapies in neurological disorders. Panel A shows the distribution of participants across the five included clinical studies. Panel B summarizes the reported time-based treatment differences in glioblastoma, including a 2.2-month progression-free survival difference and a 2.0-month overall survival difference. Panel C presents two-year progression-free survival in primary central nervous system lymphoma, showing 73% versus 51% in the primary comparison and 86% versus 71% after consolidation therapy. Panel D summarizes the direction of efficacy signals across included neurological conditions, indicating clear progression-free survival benefit in glioblastoma and primary central nervous system lymphoma, subgroup-level benefit in amyotrophic lateral sclerosis and multiple sclerosis, and no clear superiority in ischemic stroke.

DISCUSSION

This systematic review synthesized recent clinical evidence on stem cell–based and cell-associated therapeutic approaches across selected neurological disorders, including amyotrophic lateral sclerosis, glioblastoma, ischemic stroke, multiple sclerosis, and primary central nervous system lymphoma. Across the five included studies, the overall safety profile appeared acceptable, with interventions generally reported as tolerable within the trial contexts. However, efficacy was inconsistent and strongly dependent on disease condition, intervention type, outcome selection, and patient subgroup. The available evidence therefore supports cautious clinical interpretation rather than a broad conclusion that stem cell therapy is uniformly effective across neurological disorders.

The biological plausibility of stem cell therapy in neurological disease is supported by preclinical and translational evidence showing potential neuroprotective, immunomodulatory, trophic, and regenerative mechanisms (16). These mechanisms are particularly relevant in disorders characterized by neuronal loss, inflammatory damage, impaired neural repair, or progressive functional decline. Nevertheless, the clinical studies included in this review demonstrate that plausible biological mechanisms do not automatically translate into consistent therapeutic benefit. The ischemic stroke trial using MultiStem therapy showed no clear superiority over placebo in the reported day-90 clinical outcome, despite an acceptable safety profile (21). This finding highlights a central challenge in regenerative neurology: timing, patient selection, route of administration, disease stage, and outcome sensitivity may determine whether a biologically plausible therapy produces measurable clinical benefit.

In amyotrophic lateral sclerosis, the trial of mesenchymal stem cell–neurotrophic factor cells reported encouraging signals in predefined rapid progressors, including improvement in early disease progression and ALSFRS-R slope responder analysis (17). These findings are clinically important

because ALS is a progressive neurodegenerative disorder with limited disease-modifying options. However, the observed benefit was subgroup-specific rather than clearly generalizable to all participants. This distinction is essential for interpretation, because subgroup effects may identify a biologically responsive population but require confirmation in larger, adequately powered trials with prespecified responder definitions and long-term functional endpoints.

In glioblastoma, the dendritic cell vaccine ICT-107 showed a statistically significant improvement in progression-free survival, while the overall survival difference favored the intervention but was not reported as statistically significant in the supplied manuscript data (18). The stronger signal among patients with HLA-A2 antigen expression suggests that immunological and molecular markers may influence therapeutic response. This supports the growing importance of biomarker-guided patient selection in cell-based therapy, particularly where immune activation, antigen presentation, or tumor microenvironment interactions may determine clinical effect (19). However, progression-free survival benefit should be interpreted alongside overall survival, quality of life, safety, and reproducibility before making strong clinical recommendations.

In progressive multiple sclerosis, intrathecal mesenchymal stem cell-derived neural progenitor therapy showed favorable effects in patients with greater baseline disability, particularly those with EDSS scores of 6.0–6.5 (20). Reported improvements in walking performance, cerebrospinal fluid biomarkers, grey matter atrophy, and bladder function suggest that selected patients with advanced disability may derive measurable functional or biological benefit. However, as with ALS, the benefit appeared most apparent in a subgroup rather than across the entire disease spectrum. This finding reinforces the need for stratified clinical trial designs that define disease stage, disability severity, inflammatory activity, and neurodegenerative burden before treatment.

The primary central nervous system lymphoma study demonstrated higher two-year progression-free survival in the myeloablative arm than in the nonmyeloablative arm, with values of 73% versus 51%. However, the secondary comparison after consolidation therapy showed 86% versus 71% and was not statistically significant. This pattern suggests that treatment intensity may influence early disease-control outcomes, but interpretation should remain specific to the oncological and consolidation-therapy context rather than being generalized as a direct regenerative effect of neural stem cells (25). This distinction is important because PCNSL differs fundamentally from neurodegenerative and neuroinflammatory conditions, and its outcomes are survival- and malignancy-focused rather than primarily functional rehabilitation outcomes.

The findings of this review also show that the term “stem cell therapy” covers a highly heterogeneous group of interventions. The included studies varied in cell source, cell processing, mechanism of action, delivery route, comparator, target disease, and endpoint. Some interventions were mesenchymal or progenitor cell based, while others involved dendritic cell immunotherapy or consolidation approaches in malignancy. This heterogeneity limits direct comparison across studies and prevents meaningful pooled quantitative synthesis. Future reviews may need to narrow eligibility by disease category, cell type, route of administration, or outcome domain to generate more clinically actionable conclusions.

Safety remains a central consideration in cell-based therapy. Although the included trials generally reported tolerability, long-term risks remain important, including immune reactions, ectopic tissue formation, tumorigenicity, infection risk, procedural complications, and uncertainty related to repeated dosing or intrathecal administration. Ethical and regulatory concerns are also relevant, particularly because stem cell interventions are often promoted clinically before sufficient high-quality evidence is available (23, 24). Rigorous trial oversight, transparent reporting, standardized manufacturing protocols, and long-term follow-up are necessary before wider clinical adoption.

This review has several limitations. First, only five studies were included, and they addressed different neurological conditions, making direct comparison limited. Second, the extracted evidence did not

provide sufficient raw data for meta-analysis, confidence interval calculation, or standardized effect-size estimation. Third, some efficacy signals were based on subgroup or secondary endpoint findings rather than uniformly positive primary outcomes. Fourth, the screening numbers in the source manuscript require reconciliation to ensure full PRISMA consistency. Finally, risk-of-bias interpretation should be clarified, particularly where the incomplete outcome data domain was coded as “No” without an explicit definition. Despite these limitations, the review provides a clinically useful synthesis showing that stem cell–based therapies appear tolerable in selected trial settings, while efficacy remains condition-specific, subgroup-dependent, and insufficiently consistent for broad generalization.

CONCLUSION

Stem cell–based and cell-associated therapies appear generally tolerable across the included clinical studies on neurological disorders, but their therapeutic efficacy remains inconsistent and highly dependent on disease type, intervention characteristics, outcome selection, and patient subgroup. The strongest reported signals were observed in progression-free survival outcomes in glioblastoma and primary central nervous system lymphoma, while subgroup-level benefits were reported in amyotrophic lateral sclerosis and multiple sclerosis. In ischemic stroke, MultiStem therapy did not show clear superiority over placebo in the reported clinical outcome. Current evidence therefore supports continued investigation rather than routine generalized use of stem cell therapy across neurological disorders. Future trials should use larger sample sizes, standardized cell-processing protocols, prespecified responder subgroups, clinically meaningful endpoints, long-term safety follow-up, and transparent reporting to determine which patients are most likely to benefit.

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