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REVIEW

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Stem cell therapy use in patients with dementia: a systematic review

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Abstract

Background Stem cell therapy (SCT) is increasingly recognized for its potential in managing cognitive impairment, particularly that of dementia. The application of SCT aims to restore cognitive functioning in people living with dementia. Beyond pre-clinical studies, several clinical trials have evaluated specific stem cell (SC) types for their efficacy in treating dementia.

Aims & Objectives To assess the status and efficacy of pre-clinical and clinical studies utilizing SCs as a therapeutic approach for dementia.

Methods A systematic review was conducted using two electronic databases: MEDLINE and Embase. We reviewed studies on the application of SCs in dementia, focusing on the following aspects: Animal models used in pre-clinical studies, tissue sources of SCs and donor species, and administrative routes and outcome assessments. Included papers comprised randomized control trials (RCTs) and original studies, while those involving adjuvant therapies for dementia were excluded. Quality assessment criteria included relevance to the research question, type of SCs, stage of SC transplantation, duration and route of administration, methods for outcome assessment, and the total number of animals implicated.

Results A total of 32 papers were included, encompassing 21 clinical trials and 11 preclinical studies. The preclinical studies employed various transgenic animal models to evaluate SCT outcomes. Animal models of dementia, particularly transgenic mice, have proven instrumental in replicating human disease mechanisms. These models facilitate understanding of pathophysiology and preclinical testing of therapeutic interventions. Studies utilizing SCT demonstrated notable improvements in spatial memory, reduced neuroinflammation, and protection against amyloid-beta (Aβ) toxicity. Key mechanisms included modulation of inflammation, microglial immune responses, neurogenesis support, and anti-amyloidogenic effects. Preclinical studies predominantly employed human placenta-derived mesenchymal stem cells (PD-MSCs), umbilical cord-derived MSCs (U-MSCs), and induced pluripotent stem cell-derived neuronal precursors. Administration routes varied, with stereotactic and intravenous injections targeting affected brain regions. Reductions in inflammatory markers such as IL-1β, TNF-α, and increases in anti-inflammatory cytokines like IL-4 and IL-10 were observed. These outcomes emphasize the immunomodulatory and neuroprotective capacities of SCT.

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Conclusion SCT shows promise in addressing dementia-related pathologies by leveraging diverse therapeutic mechanisms. Continued refinement of preclinical models and translational research is essential to bridge gaps between preclinical findings and clinical applications, potentially paving the way for novel treatments for dementia.

Keywords Dementia, Stem cell therapy, Preclinical studies, Transgenic animal models, Neuroinflammation, Amyloid-beta

Introduction

Stem cells and their therapeutic potential

Stem cells (SCs) are undifferentiated cells with the unique ability to self-renew and differentiate into specialized cell types, making them a cornerstone of regenerative medicine [1–3]. This unique capacity allows SCs to spontaneously generate organ-specific cells under appropriate conditions, pivotal in tissue and regenerative medicine [1–3]. Among the various types of stem cells, human-induced pluripotent stem cells (hiPSCs) have emerged as a groundbreaking innovation [3]. Derived from adult somatic cells, such as fibroblasts, hiPSCs can be reprogrammed to a pluripotent state, enabling them to generate virtually any cell type in the body [3]. The advent of hiPSCs has unlocked vast potential for therapeutic applications across various diseases, including neurodegenerative disorders [1, 2].

The global burden of neurodegenerative diseases

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and other forms of dementia represent a significant and growing public health challenge [4]. According to the World Health Organization (WHO), dementia alone affects approximately 55 million individuals globally, with projections expecting it to rise to 78 million and 139 million by 2030 and 2050, respectively [5]. These conditions are characterized by the progressive loss of neuronal structure and function, leading to debilitating symptoms such as memory loss, cognitive decline, and motor dysfunction [6]. Despite decades of research, current treatments for neurodegenerative diseases remain largely palliative, focusing on symptom management rather than addressing the underlying causes of neuronal degeneration [7–9].

Limitations of current therapies

Existing therapeutic strategies for neurodegenerative diseases, such as cholinesterase inhibitors and NMDA receptor antagonists, offer only modest benefits and are often associated with significant side effects, including gastrointestinal disturbances, dizziness, and cognitive worsening [9–11]. These treatments do not halt or reverse disease progression, highlighting the urgent need for innovative approaches that target the root causes of neurodegeneration [9–11]. Stem cell-based therapies have emerged as a promising alternative, offering the potential to replace lost or damaged neurons, modulate inflammatory responses, and promote tissue repair [10, 11].

Stem cell therapy: A promising frontier

Stem cell therapy (SCT) encompasses a range of approaches, including the use of mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), human-induced pluripotent stem cells (hiPSCs), and neural stem cells (NSCs). Each of these cell types has unique properties that make them suitable for different therapeutic applications [6, 12]. For example, MSCs are known for their immunomodulatory and anti-inflammatory effects, while NSCs have the potential to differentiate into neurons and glial cells, making them particularly valuable for treating brain disorders [6, 12]. Additionally, advances in 3D cell culture techniques have led to the development of cerebral organoids, which mimic the structure and function of specific brain regions. These organoids provide a valuable platform for studying disease mechanisms and testing potential therapies in a controlled environment [12].

The role of stem cells in dementia

Dementia, a broad category of brain disorders, is characterized by impaired neuronal function, leading to symptoms such as memory loss, communication difficulties, and cognitive decline, as defined by the Dementia Society of America [13]. Alzheimer's disease, the most common form of dementia, is associated with the accumulation of amyloid-beta plaques and tau protein tangles, which disrupt neuronal communication and trigger cell death [14]. Stem cell therapy offers a promising approach to addressing these pathological changes by promoting neurogenesis, reducing inflammation, and enhancing synaptic connectivity. Preclinical studies have demonstrated the potential of SCT to improve cognitive function and reduce pathological hallmarks in animal models of dementia, paving the way for clinical translation [9–11].

Objectives of this systematic review

Recent studies underscore the potential of SCT in mitigating AD progression, demonstrating their role in tissue and regenerative medicine [9–11]. Thus, in this review, we conducted a systematic analysis to explore the potential applications of SCT in neurodegenerative diseases. By synthesizing current research, we aimed to illustrate the rapid advancements in SCT and advocate

for continued exploration of SC-based therapies to foster neurogenesis and develop innovative treatments for such challenging conditions.

Methods

The search was conducted across three major databases: MEDLINE, EMBASE, and ClinicalTrials.gov, covering studies published until July 2024. Our search strategy employed Boolean operators combining terms such as "Stem cells OR Dementia," "Mesenchymal stem cells AND Dementia," and "Treatment of Dementia AND Stem cells." To ensure reproducibility, we documented the exact search strings and filters used for each database. The search results were exported to a reference management software (EndNote X9) for deduplication and initial screening. The PRISMA flow chart (Fig. 1) provides a detailed overview of the study selection process, including the number of records identified, duplicates removed, and studies excluded at each stage.

Inclusion and exclusion criteria

Our review included randomized controlled trials (RCTs) that specifically examined the use of stem cells (SCs) as a therapeutic intervention for dementia. To maintain a focused analysis on SC-based treatments, we excluded studies investigating adjuvant therapies, such as pharmacological agents, cognitive stimulation, or non-invasive brain stimulation techniques. Additionally, studies that did not report primary outcomes related to cognitive function, behavioral changes, or neuropathological improvements were excluded. This criterion ensured that our analysis concentrated on the direct application and efficacy of SCs in addressing dementia-related neurodegeneration. Only full-text, peer-reviewed articles in English were considered.

Study selection

The study selection process was conducted in two phases: Two independent reviewers screened the titles and abstracts of all identified records to determine eligibility based on the predefined inclusion and exclusion criteria. To ensure consistency, the reviewers employed standardized screening sheets and participated in a calibration exercise prior to the screening process. Discrepancies between reviewers were resolved through discussion, and a third senior investigator was consulted when consensus could not be reached. The full texts of potentially eligible studies were independently reviewed by the same two reviewers. Employing standardized screening sheets and following a calibration exercise, the reviewers assessed the studies in duplicate to ensure accuracy. Studies that met the inclusion criteria were selected for data extraction, while those that did not meet the criteria were excluded, with reasons for exclusion documented for transparency.

Data extraction and quality assessment

Data extraction was performed using a standardized template to ensure consistency across studies. Two reviewers independently extracted data from the included studies, and discrepancies were resolved through discussion. The following key parameters were extracted:

1. Study Characteristics: Author, year, country, study design, and sample size.
2. Intervention Details: Type of stem cells used (e.g., MSCs, ESCs, hiPSCs, NSCs), species and tissue sources, stage of transplantation, duration and route of administration, and dosage.
3. Outcome Measures: Cognitive function improvements, behavioral changes, neuropathological outcomes, and safety profiles.
4. Study Quality Indicators: Randomization, blinding, and transparency in reporting key study details.

Quality assessment criteria included adherence to the research question and transparency in reporting key study details. The quality assessment was conducted independently by two reviewers, and discrepancies were resolved through discussion.

Data analysis

The collected data were analyzed through a systematic approach to assess the efficacy and outcomes of SCT in both pre-clinical and clinical settings. The qualitative data from the included studies, including descriptions of cognitive function improvements, behavioral changes, and neuropathological outcomes, were systematically reviewed and synthesized. Findings were categorized by stem cell type, disease stage, and route of administration to identify trends and patterns in therapeutic effects. The results were compared across different studies to identify trends and patterns in the therapeutic effects of SCT. Data from pre-clinical studies, including animal models, stem cell sources, and treatment outcomes, were systematically reviewed and synthesized to evaluate their translational potential to human clinical applications. Findings were categorized by animal model (e.g., transgenic mice, rat models of AD) and outcome measures (e.g., amyloid-beta reduction, synaptic plasticity improvements).

Results

We searched Medline, Embase, and ClinicalTrials.gov databases, identifying a total of 4419 studies (4287 from Medline and Embase, and 132 from ClinicalTrials.gov). After removing duplicates, 4104 articles were screened by title and abstract, resulting in 436 potentially relevant

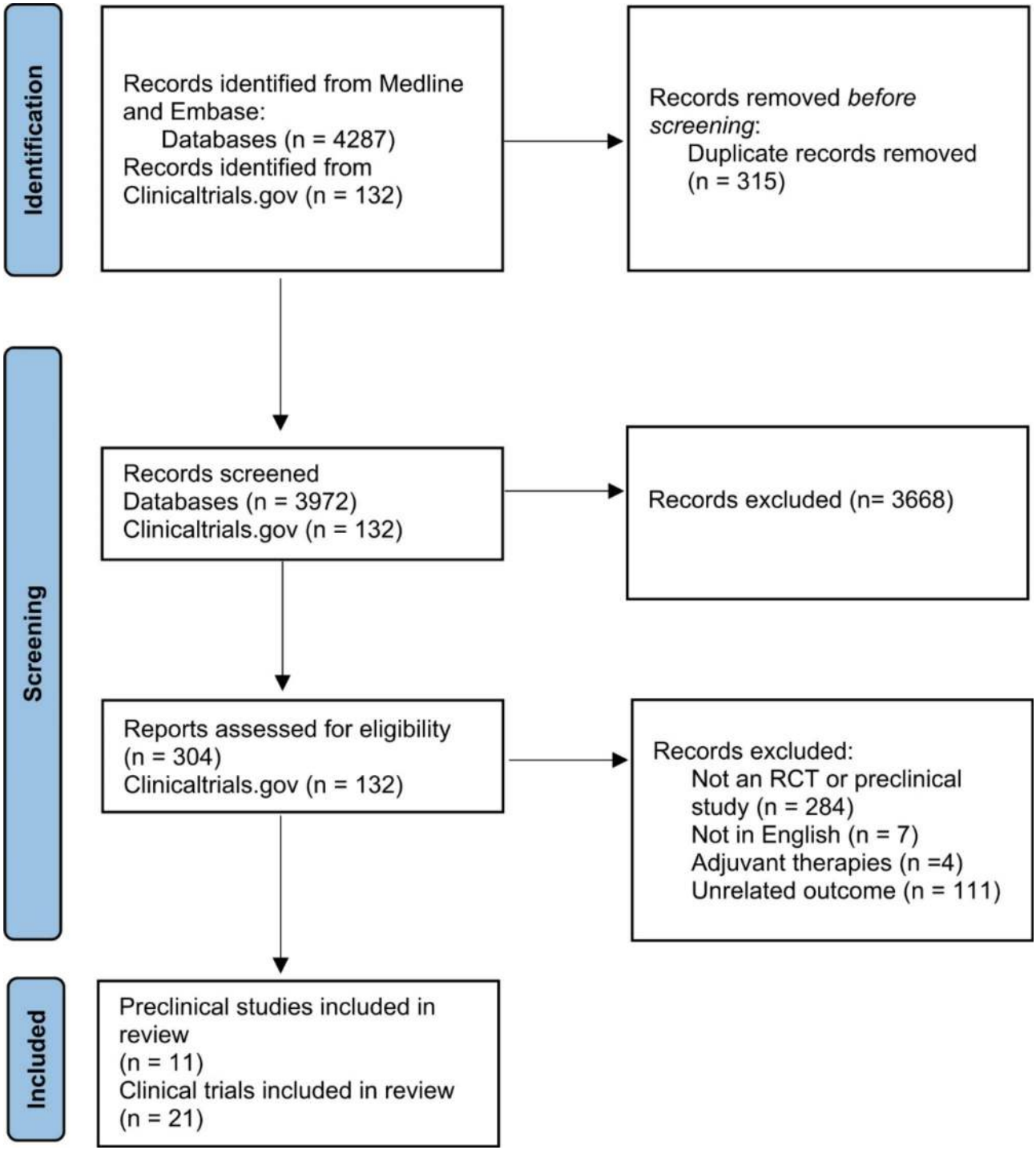


Fig. 1 PRISMA Flow diagram
Abbreviations: RCT: Randomized Clinical Trial

studies. Following full-text screening, 32 studies met our inclusion criteria, including **21 clinical trials** and **11 preclinical studies**. Refer to Fig. 1 for a detailed description (Fig. 1). This study was also registered in PROSPERO under the number **CRD42025640270**. A title and abstract screening was performed according to PRISMA standards (the link below): https://www.crd.york.ac.uk/PROSPERO/view/CRD42025640270.

Pre-Clinical studies

Dementia represents the foremost etiology of disability among individuals aged over 65 years, with its prevalence

steadily increasing. Current therapeutic options fail to address key symptoms like psychomotor agitation, aggression, depression, and reduced physical activity [15]. Behavioral and psychological symptoms afflict at least 90% of dementia patients [15]. Given the absence of definitive pharmacological interventions, elucidating disease pathophysiology and exploring novel therapeutic agents are paramount. Animal models serve as indispensable tools in these endeavors [16]. Continued refinement of these models through ongoing research promises to bridge the translational dearth between preclinical findings and clinical applications [16].

Effective animal models must rigorously replicate human disease mechanisms to facilitate the development of efficacious treatments. Small animal models, such as mice and rats, offer distinct advantages including cost-effectiveness, reproducibility, and suitability for investigating related human pathophysiology and therapeutic pathways [17]. Animal models of AD encompass spontaneous, interventional, and genetically modified varieties [16]. However, while spontaneous models hold appeal, they pose challenges comprising the risk of zoonoses, maintenance costs, and variability in reproducibility due to extended lifespans [16].

Advances in genetic manipulation have facilitated the development of transgenic animal models that exhibit characteristics akin to AD, particularly in mice, preferred for their ease of genetic modification and shorter lifespans [16]. Rats, with physiological similarities closer to humans, offer advantages in studying motor behaviors but are hindered by technical limitations in genetic engineering [16]. For appropriate interpretation of study results, the influence of the genetic background on transgenic phenotypes must be carefully considered [16].

Animal models not only deepen our understanding of disease pathophysiology but also serve as essential tools for preclinical validation of potential therapeutic interventions [18]. Over the past two decades, substantial progress has been made in refining animal models for dementia research and evaluating therapeutic candidates [19].

Table 1 summarizes the outcomes of preclinical studies utilizing various SCT for the management of dementia in transgenic mouse models [20–24]. The table categorizes SCT based on different cell classes, including Human PD-MSCs, Human U-MSCs, and others, each tested in specific transgenic models, that of B6C3-Tg (APPswe/PSEN1dE9) and Tg2576 (APPswe). Injection types varied, encompassing intravenous and stereotactic approaches, tailored to target affected brain regions effectively.

Outcomes observed across studies predominantly focused on improvements in spatial memory, assessed through tasks like the Morris water maze and novel object recognition tests. Additionally, reductions in inflammatory markers such as interleukins (ILs) and tumor necrosis factor (TNF) were reported, indicating potential neuroprotective effects. Mechanistic insights highlighted included neurotrophic support, modulation of microglial responses, and protection against amyloid-beta (Aβ) neurotoxicity, underscoring the multifaceted approaches of SCT in mitigating dementia-related pathologies.

Table 2 presents a detailed overview of SCT outcomes in dementia therapeutics, specifically focusing on diverse transgenic mouse models and their responses to various SC types [25–30]. The table categorizes SCT based on cell classes such as Human PD-MSCs, Human U-MSCs, and others, each evaluated in models including

Table 1 Overview of preclinical studies on stem cell therapy for dementia in Transgenic mouse models

Cell Class	Murine embryonic NSCs (20)	Human foetal NSCs (21–23)			Human UCB-MSCs (24)
Transgenic Mice Model	B6C3-Tg (APPswe/PSEN1dE9)(20)	NSE-APPswe (21)	Tg2576 (APPswe) (22)	3×Tg-AD, CaM/Tet-DTA (23)	APP/PS1 (24)
Stereotactic Injection Type	Bilateral intra-hippocampal	Bilateral intraventricular	Bilateral intra-hippocampal	Bilateral intra-hippocampal	Three bilateral intra-hippocampal
Outcomes	Improved spatial memory (Morris water maze) Decreased expression of pro-inflammatory cytokines	Improved spatial memory (Morris water maze) Decreased expression of pro-inflammatory cytokines	Improved spatial memory (Morris water maze)	Improved spatial memory (Morris water maze, context- and place-dependent NOR task)	Improved spatial memory (Morris water maze) Reduced levels of pro-inflammatory cytokines
Mechanism	Modulation of inflammation	- Modulation of inflammation - Microglia immune response - Protection from Aβ neurotoxicity	Neurotrophic support of endogenous neurogenesis and synaptic connectivity	Neurotrophic support of endogenous neurogenesis and synaptic connectivity	- Modulation of inflammation - Microglia -Anti-amyloidogenic

Abbreviations: Aβ: amyloid-beta; AD: Alzheimer's disease; AD-MSC: adipose-derived mesenchymal stem cell; BM-MSC: bone marrow-derived mesenchymal stem cell; COX: cyclooxygenase; GABA: gamma-aminobutyric acid; IL: interleukin; iNOS: inducible nitric oxide synthase; iPSC: induced pluripotent stem cell; NSC: neural stem cell; PBS: phosphate-buffered saline; PD-MSC: placenta-derived mesenchymal stem cell; PGE: prostaglandin E; PTGER: prostaglandin E receptor; TNF: tumor necrosis factor; U-MSC: umbilical cord Warton's jelly-derived mesenchymal stem cell; UCB-MSC: umbilical cord blood-derived mesenchymal stem cell

Table 2 Comprehensive analysis of stem cell therapy outcomes in dementia treatment: Transgenic mouse models and stem cell types

Cell Class	Human PD-MSCs [25]	Human U-MSCs Human U-MSC-NCs [26]	Human A-MSCs [27]	Murine BM-MSCs [28]	Human BM-MSCs [29]	Human iPSC-derived neuronal precursors [30]
Transgenic Mice Model	Aβ1–42 cerebrally infused	B6C3-Tg (APPswe/PSEN1dE9)	Tg2576 (APPswe), 3xTg-AD	APP/PS1	Aβ1–42 cerebro-ventricular infused	PDAPP
Injection Type	Intravenous	Bilateral intra-hippocampal stereotactic	Intravenous	Intravenous	Intravenous	Bilateral intra-hippocampal stereotactic
Outcomes	Improved spatial memory (Morris water maze) Reduced expression of inflammatory proteins iNOS and COX-2, and an array of pro-inflammatory cytokines	Improved spatial memory (Morris water maze) Reduced pro-inflammatory cytokines (IL-1β and TNF-α), and increased anti-inflammatory cytokine IL-4 in the U-MSC-NC	Improved spatial memory (Morris water maze) Reduced pro-inflammatory cytokines IL-1 and TNF-α at week 1 Increased anti-inflammatory cytokines IL-10 and TNF-β at week 12	Reduced levels of hippocampal TNF-α, IL-6, and elevated levels of hippocampal PTGER2	Improved working memory performance (Radial Arm Maze)	Improved spatial memory (Morris water maze) 45 days post-operation Improved spatial memory (Morris water maze)
Mechanism	-Neurotrophic support of endogenous neurogenesis -Modulation of inflammation - Microglia immune response. - Anti-amyloidogenic	-Modulation of inflammation -Microglia immune response	- Modulation of inflammation - Microglia immune response	- Modulation of microglial immune response	-Neurotrophic support of endogenous neurogenesis - Protection from Aβ neurotoxicity	Regeneration of depleted neural networks

Abbreviations: Aβ: amyloid-beta; AD: Alzheimer's disease; AD-MSC: adipose-derived mesenchymal stem cell; BM-MSC: bone marrow-derived mesenchymal stem cell; COX: cyclooxygenase; IL: interleukin; iPSC: induced pluripotent stem cell; NSC: neural stem cell; PD-MSC: placenta-derived mesenchymal stem cell; PGE: prostaglandin E; PTGER: prostaglandin E receptor; TNF: tumor necrosis factor; U-MSC: umbilical cord Warton's jelly-derived mesenchymal stem cell; U-MSC-NC: neuron-like cell differentiated from umbilical cord Warton's jelly-derived mesenchymal stem cell; UCB-MSC: umbilical cord blood-derived mesenchymal stem cell

Aβ1–42-infused and specific transgenic strains like that of B6C3-Tg (APPswe/PSEN1dE9) and Tg2576 (APPswe).

Injection methods varied and included intravenous and stereotactic administration, both tailored to optimize therapeutic delivery and efficacy in experimental contexts. Reported outcomes predominantly highlighted improvements in spatial memory performance, often assessed using the Morris water maze test. Additionally, reductions in pro-inflammatory cytokines such as IL-1β and TNF-α, coupled with increases in anti-inflammatory cytokines like IL-4 and IL-10, underscored the immunomodulatory effects of SCT in mitigating neuroinflammation.

Mechanistic insights elucidated included neurogenesis support, modulation of microglial immune responses, and protection against Aβ-induced neurotoxicity, emphasizing the diverse therapeutic mechanisms employed by SCT in combating dementia pathology.

Clinical studies involving stem cell therapy in dementia cases

Several clinical trials investigating SCTs for dementia are currently at different stages. Our review identified 21 trials, of which 6 have been completed, with results available for 4. Six trials are actively recruiting or awaiting initiation, while the statuses of 6 trials were undisclosed, 2 trials withdrawn, and 1 trial no longer available. Most trials examined employed human MSCs delivered via intravenous, intracerebral, and intraventricular routes, with intranasal administration also under exploration for its potential benefits. Table 3 summarizes these trials, detailing their recruitment status, phase, cell type, route of administration, and key findings.

Among the completed trials, NCT01297218 investigated the employment of human UCB-MSCs administered via intracerebral infusion [30]. The study reported acute adverse events in all nine subjects during a 12-week follow-up period, with no serious adverse events observed over a 24-month follow-up. Importantly, no dose-limiting toxicities were reported, highlighting the safety profile of this approach [30]. In contrast, the trial registered under NCT02054208 [31], which utilized human UCB-MSCs administered via intraventricular infusion, reported acute adverse events within 36 h of administration. The most common adverse events included fever ($n=9$), headache ($n=7$), nausea ($n=5$), and vomiting ($n=4$), all of which resolved spontaneously within 36 h. Serious adverse events were observed in three participants; however, no dose-limiting toxicities were reported [31].

Several ongoing trials are exploring different SCT approaches. For instance, NCT03724136 is currently recruiting participants to investigate the use of BM-MSCs administered via intravenous fractionation, with results yet to be published [32]. Similarly, NCT04388982 aims to evaluate the efficacy of MSC-derived exosomes

Table 3 Status and findings of clinical trials on stem cell therapy in dementia

NCT	Status	Phase	Cell Type	Route	Findings
NCT01297218 [30]	Completed	1	Human UCB-MSCs	IC Infusion	Acute adverse events in all 9 subjects during a 12-week follow-up No serious adverse events in a 24-month follow-up No dose-limiting toxicity
NCT03724136 [32]	Recruiting	-	BMSC	IV Fraction	Not yet published
NCT04388982 [33]	Unknown	1/2	MSCs-Exos	Nasal drip	Not yet published
NCT04040348 [41]	Completed	1	Allogeneic human UCB-MSCs	IC Infusion	Not yet published
NCT01696591 [42]	Unknown (follow-up study)	-	-	-	Not yet published
NCT02795052 [43]	Recruiting	-	BMSCs	IV and intranasal infusion	Not yet published
NCT04228666 [34]	Withdrawn (Due to COVID-19 Pandemic)	1/2	HB-adMSCs	IV infusion	N/A
NCT04855955 [44]	No Longer Available	-	Autologous human AD-MSCs	-	Not yet published
NCT02672306 [45]	Unknown	1/2	Human UCB-MSCs	IV infusion	Not yet published
NCT01547689 [46]	Unknown	1/2	Human UCB-MSCs	IV infusion	Not yet published
NCT02054208 [31]	Completed	1/2a	Human UCB-MSCs	IVT infusion	Acute adverse events within 36 h Serious adverse events in 3 subjects No dose-limiting toxicity
NCT02600130 [47]	Completed	1	LMSCs	IV infusion	Not yet published
NCT04954534 [48]	Unknown (follow-up study)	-	-	-	Not yet published
NCT03117738 [35]	Completed	1/2	Autologous Ad-MSCs	IV infusion	Serious adverse events in 3 out of 11 subjects Other adverse events in 3 out of 11 subjects
NCT03172117 [49]	Completed (follow-up study)	-	-	-	All patients had adverse events
NCT02912169 [50]	Withdrawn (company dissolved)	1/2	Autologous AD-SVF	IV and intranasal infusion	Not yet published
NCT04482413 [51]	Not yet recruiting	1/2b	Autologous ADSCs	IV infusion	Not yet published
NCT03297177 [52]	Unknown	1/2	Autologous micro-vasculature stem/ stromal cells	IV infusion	N/A
NCT03899298 [53]	Not yet recruiting	1	Human UCB-MSCs	IV, intranasal, nebulizer dependent on patient condition	Not yet published
NCT04684602 [54]	Recruiting	1/2	Human UCB-MSCs	IV, intranasal, nebulizer dependent on patient condition	Not yet published
NCT02899091 [55]	Active, not recruiting	1/2	Human UCB-MSCs	IV infusion	Not yet published

Abbreviations: UCB-MSCs: Umbilical Cord Blood Mesenchymal Stem Cells; BMSCs: Bone Marrow Stem Cells; MSCs-Exos: Exosomes from Allogenic Adipose Mesenchymal Stem Cells; HB-adMSCs: Hope Biosciences Autologous Mesenchymal Stem Cells; AD-MSCs: Adipose-Derived Mesenchymal Stem Cells; LMSCs: Longeveron Mesenchymal Stem Cells; and AD-SVF: Autologous Adipose-Derived Stromal Vascular Fraction

administered via nasal drip, with results pending publication [33]. A notable withdrawal due to the novel coronavirus disease 2019 (COVID-19) pandemic is documented in NCT04228666, which planned to investigate the application of Hope Biosciences' autologous A-MSCs via intravenous infusion [34]. The trial was halted without published findings [34]. Moreover, trials such as NCT03117738, utilizing autologous A-MSC via intravenous infusion, reported serious adverse events in three out of eleven subjects, underscoring the importance of rigorous safety monitoring in SCT trials [35].

In summary, although a number of clinical trials have shown encouraging results about the safety and possible effectiveness of SCT in the management of dementia, variability in outcomes and difficulties like adverse events require ongoing research and standardized methodologies to advance SCT as a viable therapeutic option.

Table 4 Diverse types of stem cells utilized in human clinical trials for neurodegenerative disorders [40]

Categories	Cell Types	Source	Advantages	Disadvantages
Pluripotent stem cells	Human embryonic stem cells (hESCs)	Inner cell mass of the blastocyst	A good source for cell-replacement therapy.	Challenge of phenotype instability, poor survival of transplanted cells and possible tumour formation
			Can generate neuronal phenotypes for clinical treatment of neurological disorders	Progressive research is impeded by regulatory policies due to ethical controversies
	Human-induced pluripotent stem cells (hiPSCs)	Epiblast layer of an implanted embryo Induced adult human fibroblasts	Can serve as cell models of neurodegenerative disorders in vitro Important in autologous transplantation to reduce immunogenicity	Cells are derived from a patient and may carry any genetic defects specific to said patient
Multipotent stem cells	Human neural stem cells (hNSCs)	Foetal, neonatal or adult brain	Useful in treating neurodegenerative disorders	Require the presence of growth factors even in vitro
		Directed differentiation of pluripotent stem cells	Has a lower risk of causing tumour formation	May not yield high proliferative capacity in expansive in vitro stem cell studies
	Neural crest stem cells (NCSCs)	Dorsal margins or neural folds during embryogenesis	Do not require immunosuppressants as the patient's cells can be used	Has limited ability to differentiate and undergo self-renewal
	Olfactory ensheathing cells (OECs)	Neuroglia of olfactory axon bundles	Capable of repairing neural bundles with myelin defects and regenerating axons	Prospects of clinical use are limited to the CNS
	Haematopoietic stem cells (HSCs)	Bone marrow Umbilical cord blood Foetal tissues (Liver, Spleen)	Have the immense capacity to proliferate and differentiate into various cell lineages	Challenges with potency and number of cells obtained, especially when umbilical cord blood is the source
Human Mesenchymal Stem Cells (hMSCs)	BMSCs	Adult bone marrow	Secrete various anti-inflammatory and antiapoptotic cytokines, which aid healing and tissue repair in neurological disorders	Challenges with consensus on appropriate dosing and route of administration
	UCB-MSCs	Umbilical cord blood		
	MSCs-Exos	Peripheral blood	Possess the ability to migrate to injury sites and initiate neurorestorative functions	Underlying mechanisms of action are not fully understood
	LMSCs			
	HB-adMSCs	Adipose tissue		
	AD-MSCs			
	AD-SVF			

Abbreviations: hESCs: Human embryonic stem cells; hiPSCs: Human-induced pluripotent stem cells; hNSCs: Human neural stem cells; NCSCs: Neural crest stem cells; OECs: Olfactory ensheathing cells; HSCs: Haematopoietic stem cells; BMSCs: Bone marrow-derived mesenchymal stem cells; UCB-MSCs: Umbilical cord blood-derived mesenchymal stem cells; MSCs-Exos: Mesenchymal stem cell-derived exosomes; LMSCs: Longeveron mesenchymal stem cells; HB-adMSCs: Hope Biosciences autologous mesenchymal stem cells; AD-MSCs: Adipose-derived mesenchymal stem cells; AD-SVF: Adipose-derived stromal vascular fraction

Pre-clinical studies have extensively assessed the safety and efficacy of SCT using murine models, yet translating these findings into clinical trials has been limited. This discrepancy stems from the complex ethical considerations and uncertainties circumventing the safety of stem cell transplantation in human subjects. Globally, regulatory frameworks and policy interventions govern the funding and conduct of human clinical trials involving SCT [36, 37]. Selecting the appropriate cell source and type is crucial for enhancing the success of SCT. Notably, MSCs are favored in clinical trials targeting neurodegenerative diseases due to their ability to differentiate into non-hematopoietic stromal and neural cell lines, alongside their low immunogenicity [38, 39].

Table 4 provides a comprehensive overview of various SC types investigated in human clinical trials for neurodegenerative disorders [40]. Pluripotent stem cells (PSCs), such as that of human-induced embryonic stem cells (hiESCs) and hiPSCs, offer potential for cell-replacement therapy and modeling neurodegenerative diseases in vitro [40]. However, challenges include phenotype instability and ethical controversy which hinder their widespread application [40]. Multipotent stem cells like that of NSCs and neural crest stem cells (NCSCs) present advantages such as neuroregenerative capabilities without the need for immunosuppressants, yet they face limitations in differentiation potential and self-renewal capacity. Additionally, MSCs derived from bone marrow and the blood of the umbilical cord are extensively studied for their anti-inflammatory properties and potential in tissue repair [40]. Nevertheless, optimal dosing and administration routes remain unresolved issues due to several factors [40]. The optimal dosing and routes of administration for mesenchymal stem cells (MSCs) remain unresolved due to several factors. MSCs derived from different sources (e.g., bone marrow, adipose tissue) exhibit variability in properties, making standardization difficult [40]. Additionally, the survival

and distribution of MSCs vary depending on the delivery route, such as intravenous or intracerebral injection, with systemic delivery often resulting in low cell homing to the target site [40]. The dynamic inflammatory environment post-injury further complicates timing and effectiveness. Moreover, the lack of large-scale clinical trials with standardized protocols hinders the establishment of evidence-based guidelines [40]. These findings highlight the diverse landscape of SC types under investigation, each presenting unique advantages and challenges in advancing neuroregenerative therapies.

Quality assessment

All 32 articles collected were thoroughly analyzed for adherence to the research question.

Various types of stem cells were investigated across clinical and preclinical studies:

- BM-MSCs: Bone Marrow-Derived Mesenchymal Stem Cells.
- iPSCs: Induced Pluripotent Stem Cells.
- NSCs: Neural Stem Cells.
- PD-MSCs: Placenta-Derived Mesenchymal Stem Cells.
- U-MSCs: Umbilical Cord Warton's Jelly-Derived Mesenchymal Stem Cells.
- U-MSC-NCs: Neuron-like Cells differentiated from Umbilical Cord Warton's Jelly-Derived Mesenchymal Stem Cells.
- UCB-MSCs: Umbilical Cord Blood-Derived Mesenchymal Stem Cells.
- MSCs-Exos: Exosomes from Allogenic Adipose Mesenchymal Stem Cells.
- HB-adMSCs: Hope Biosciences Autologous Mesenchymal Stem Cells.
- AD-MSCs: Adipose-Derived Mesenchymal Stem Cells.
- LMSCs: Longeveron Mesenchymal Stem Cells.
- AD-SVF: Autologous Adipose-Derived Stromal Vascular Fraction.

The age of recruited subjects for the trials was unspecified in the literature and thus not included in the review.

Stem cells were administered via various routes:

- Bilateral intra-hippocampal stereotactic injection.
- Bilateral intraventricular stereotactic injection.
- Intravenous infusion.
- Intracerebral infusion.
- Intraventricular infusion.
- Intranasal infusion.

The duration of administration was not specified in the reviewed works.

Methods used to evaluate outcomes in stem cell trials included:

- Donor cell migration and differentiation.
- Spatial memory.
- Levels of phosphorylated tau proteins and amyloid β-plaques.
- Expression of pro-inflammatory cytokines.
- Levels of neural microglia.
- Severity of adverse events.
- Dose-limiting toxicity.

The number of animals implicated for stem cell transplantation was not specified in the review.

Discussion

Given the increasing global prevalence of dementia, AD remains a major area of research for developing effective treatments. SCTs have shown promise in promoting neuroprotection, enhancing neurogenesis, and modulating inflammatory responses in the brain. This review aims to evaluate the status and efficacy of preclinical and clinical studies involving stem cells as a therapeutic approach for AD, highlighting both advances and challenges in the field.

Mechanisms and efficacy of SCTs

Our review reveals that MSCs derived from sources such as human placenta and umbilical cord show neuroprotective effects in preclinical studies, with improvements in memory and reductions in inflammation. These findings align with the current literature, which suggests that MSCs exert their effects through various mechanisms, such as the release of neurotrophic factors, reduction in amyloid-beta toxicity, and modulation of immune responses [56]. However, despite consistent evidence of the benefits of MSCs, the precise molecular pathways through which these therapies act remain unclear. While several studies support the neurotrophic effects of MSCs [57, 58], the complex interaction between these factors and the neurodegenerative processes in AD needs further investigation.

Compared to other therapeutic strategies, such as anti-amyloid antibody treatments or small molecule drugs, SCTs offer a more comprehensive approach. Traditional treatments typically target a single pathological mechanism (e.g., amyloid-beta or tau aggregation), while SCTs may address multiple aspects of AD pathology, including neuroinflammation and cell regeneration [59, 60]. This multi-faceted approach could provide broader therapeutic benefits, especially for AD, which involves complex, interconnected processes. However, the complexity of these mechanisms poses a challenge for translating SCTs into clinical practice, as their effects may vary depending

on the type of stem cells, delivery methods, and disease stage.

Safety and clinical outcomes

The clinical trials reviewed in this study generally demonstrate a favorable safety profile for SCTs, particularly when cells are delivered through less invasive methods like intravenous infusion. This mirrors findings in other studies, where stem cell-based treatments are generally considered safe, especially when autologous or well-characterized allogeneic cells are used [61, 62]. However, as noted in our review, certain delivery methods, such as intracerebral or intraventricular injections, are associated with higher risks, including infection or immune response. This observation is consistent with previous studies, which highlight the risks linked to direct central nervous system administration of stem cells [31, 63, 64].

Despite the generally positive safety profile, variability in clinical outcomes is evident. Some trials report favorable cognitive improvements, while others show limited efficacy, reflecting the challenges of SCTs in neurodegenerative diseases. To date, only a limited number of trials have been completed, revealing challenges in achieving a sustained cognitive improvement among dementia populations. For instance, a study by He et al. (2017) noted initial cognitive gains three months post-transplantation with human UCB-MSCs, as assessed by the Mini-Mental State Exam (MMSE) and Barthel Index scoring system [65]. However, these gains regressed to baseline levels by six months, attributed to factors such as insufficient cell infusion and advanced dementia stages at study entry [65]. This underscores the complexity of translating successful preclinical outcomes to human trials and highlights the need for refined cellular models in future clinical research.

While some studies show significant cognitive improvements and behavior changes [66, 67], others yield inconclusive results [68]. This variability can be attributed to factors like patient heterogeneity, stem cell types, and differences in cognitive assessments used in trials [66, 67]. Standardizing methodologies and patient populations in future trials is essential to draw more definitive conclusions about SCT efficacy [68]. Despite the promising preclinical results, clinical translation remains challenging. A recent trial by Kim et al. (2015) showed minimal therapeutic improvements with MSCs delivered via stereotactic injection over a 24-month follow-up period [30] Similarly, other trials report modest cognitive and behavioral improvements, highlighting the difficulty of translating preclinical success into clinical outcomes [69, 70]. In contrast, intravenous (I.V.) administration of MSCs has shown better results, improving inflammation and neurocognitive function with lower doses compared to stereotactic injection [69, 70]. However, variability in factors such as MSC source, dosage, and delivery method complicates drawing definitive conclusions, although local injections may reduce systemic loss and enhance targeted effects [69, 70].

Future perspectives of stem cell therapy in treating dementia

In 2015, there were 46.8 million dementia patients globally, a number expected to reach 131.5 million by 2050 [71]. SC research has revitalized hopes for managing neurodegenerative diseases. Experimental studies employing animal models have demonstrated promising results, sparking increasing interest in the potential of SCT as a treatment for these conditions [72]. The global SCT market, valued at $10.9 billion in 2010, surged to $51.26 billion by 2017 [72].

MSCs, including those derived from adipose tissue and umbilical cord blood, are emerging as viable candidates for SCT, contrasting with the challenges associated with neural stem cells NSCs. BM-MSCs are difficult to extract and cultivate, limiting their clinical utility. Despite these challenges, recent studies highlight AD-MSCs and UCB-MSCs as promising therapies for AD and other neurodegenerative disorders. However, ESCs pose risks such as immune rejection and tumorigenesis, which complicate their therapeutic application [73].

While preclinical findings are promising, significant hurdles must be overcome before SCT can be tailored into effective treatments for dementia. Decades of research have underscored the potential of SC therapies to revolutionize treatments for conditions like multiple sclerosis, PD, and age-related macular degeneration. However, the unique nature of SC-based therapeutics raises complex policy and regulatory challenges. Healthcare authorities must develop robust legislative frameworks to support the ethical and safe progression of SC research, particularly in the context of treating dementia. In summary, the field of SC research for the management of dementia has a bright future ahead of it, but careful monitoring and regulatory assistance are needed to guarantee the safe and efficient development of novel therapeutics.

Limitations

Despite the comprehensive approach taken in this review, several limitations must be acknowledged. Firstly, the included studies exhibited significant heterogeneity in terms of study design, stem cell types, routes of administration, dosages, and outcome measures. This heterogeneity limited our ability to perform a formal meta-analysis and may have introduced variability in the findings. Additionally, there is a potential for publication bias, as studies with positive results are more likely to be published than those with negative or inconclusive

findings, which could lead to an overestimation of the effectiveness of SCT in treating dementia. Ethical and practical constraints may have limited the scope and execution of some studies, particularly in patient recruitment and the use of certain SC types. The absence of longitudinal data tracking patients over extended periods reduces the ability to assess the durability and progression of treatment effects. Lastly, most of the included studies were conducted in specific regions and may not represent the global population, with variations in genetic, environmental, and healthcare factors potentially influencing the outcomes and applicability of SCT in different populations.

Conclusion

Our review sheds light on the landscape of clinical and pre-clinical trials investigating SCT for managing dementia. Pre-clinical trials using animal models have shown promising results, indicating the potential of SCT in dementia treatment. There is a growing interest in conducting clinical trials to further explore SCT applications in human subjects. However, the outcomes of current clinical trials suggest that significant success in treating complex medical conditions like dementia with SCT has not yet been achieved. Therefore, pre-clinical trials, while informative, may not reliably predict success and efficacy in human clinical trials. Moving forward, there is a critical need for improved clinical trial methodologies and advanced models in stem cell research to delineate the most effective approaches for treating dementia. Continued research and rigorous clinical investigation are essential to realize the potential of SCT in addressing the challenges of neurodegenerative diseases.

Abbreviations

Aβ	amyloid-beta
AD	Alzheimer's disease
AD-MSC	adipose-derived mesenchymal stem cell
AD-SVF	autologous adipose-derived stromal vascular fraction
BM-MSC	bone marrow-derived mesenchymal stem cell
COVID	novel coronavirus disease 2019
COX	cyclooxygenase
CNS	central nervous system
ESC	embryonic stem cell
HB-adMSC	Hope Biosciences autologous mesenchymal stem cell
HD	Huntington's disease
hiESC	human-induced embryonic stem cell
hiPSC	human-induced pluripotent stem cell
IL	interleukin
iPSC	induced pluripotent stem cell
LMSCs	longeveron mesenchymal stem cell
PD	Parkinson's disease
PDMSC	placenta-derived mesenchymal stem cell
PGE	prostaglandin E
PSC	pluripotent stem cell
PTGER	prostaglandin E receptor
MMSE	Mini-Mental State Exam
MSC	mesenchymal stem cell
MSC-Exos	exosomes from allogenic adipose mesenchymal stem cell
NCSC	neural crest stem cell
NSC	neural stem cell
RCT	randomized control trial
SC	stem cell
SCT	stem cell therapy
SR	systematic review
TNF	tumor necrosis factor
U-MSC	umbilical cord Warton's jelly-derived mesenchymal stem cell
U-MSC-NC	neuron-like cell differentiated from umbilical cord Warton's jelly-derived mesenchymal stem cell
UCB-MSC	umbilical cord blood-derived mesenchymal stem cell
WHO	World Health Organization

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Registration on Prospero

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