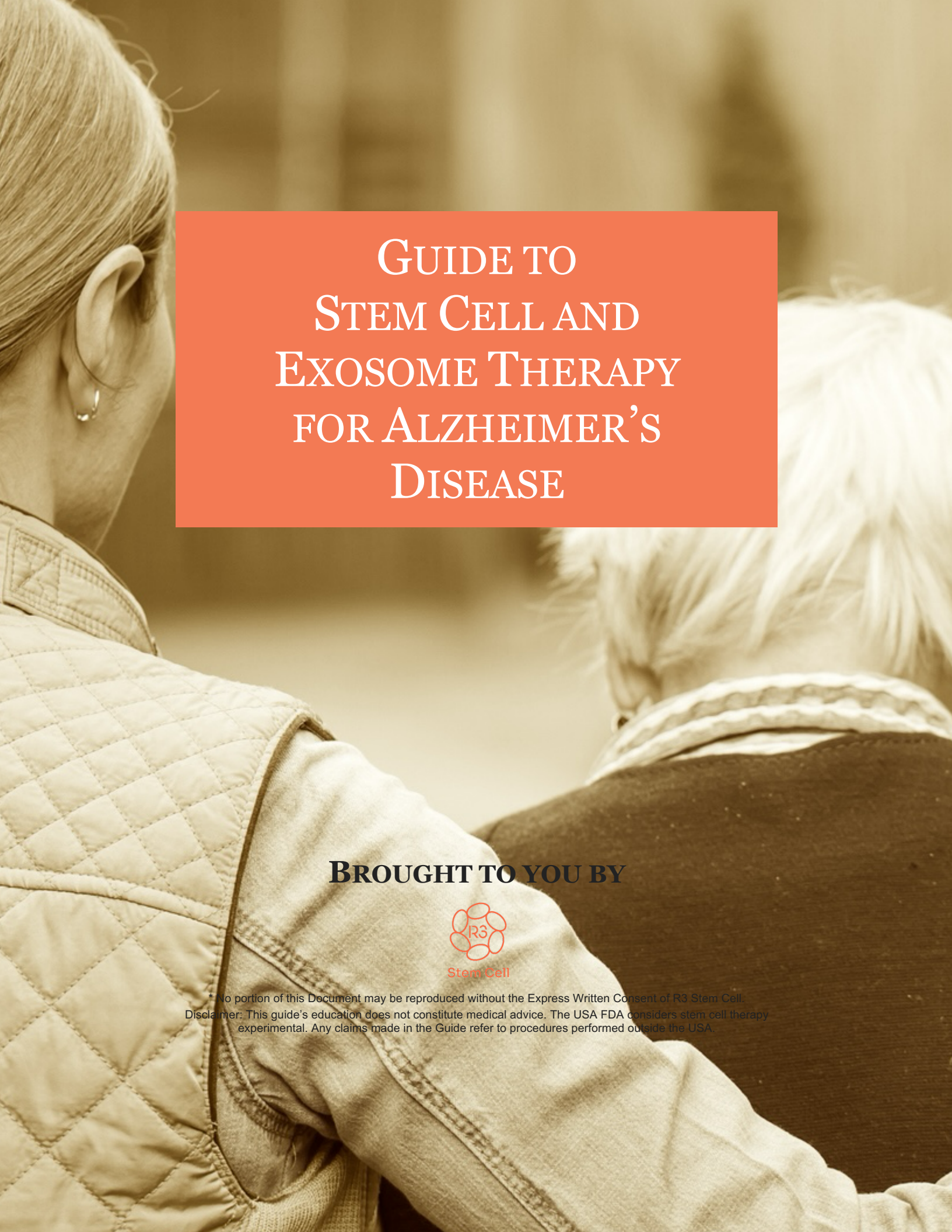




GUIDE TO STEM CELL AND EXOSOME THERAPY FOR ALZHEIMER'S DISEASE

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Guide to Stem Cell and Exosome Therapy for Alzheimer's Disease

Every day, R3 Stem Cell receives inquiries from families worldwide asking whether stem cell therapy can help a loved one with Alzheimer's disease (AD). It is one of the most hopeful and fastest-moving areas of regenerative medicine: in 2025, a randomized, placebo-controlled trial of donor mesenchymal stem cells for Alzheimer's was published in *Nature Medicine*. In this guide, we'll go through the basics of how stem cells and exosomes work in the brain, what the latest research shows, and what to expect with a regenerative procedure.

Conventional treatments for AD can ease symptoms or modestly slow decline, but none can repair damaged brain tissue. That is why there is so much interest in stem cell and exosome therapies, which target inflammation, blood flow and the brain's own repair systems.

A Significant Global Issue

Alzheimer's disease is the most common cause of dementia, accounting for an estimated 60–70% of cases. The World Health Organization estimates that about 57 million people worldwide were living with dementia in 2021, with nearly 10 million new cases every year. In the United States alone, more than 7 million people aged 65 and older are living with Alzheimer's, and that number will keep rising as the population ages.

AD is a progressive neurodegenerative disease. It usually begins with subtle memory lapses and gradually affects language, judgment, planning, orientation and, eventually, the ability to carry out everyday activities. Behavioral and psychological changes such as anxiety, depression, agitation, apathy and sleep disturbances are also common, and are often among the hardest symptoms for families.

The disease typically moves through stages, from mild cognitive impairment (MCI) to mild, moderate and severe dementia. Changes in the brain begin years, sometimes decades, before the first symptoms appear, which is why earlier intervention is a major focus of current research.

What are the reasons Alzheimer's Disease occurs?

Two hallmark changes define AD in the brain. The first is amyloid plaques, clumps of a protein fragment called beta-amyloid that build up between nerve cells. The second is neurofibrillary tangles, twisted strands of a protein called tau that accumulate inside nerve cells and disrupt their internal transport system. Over time, synapses are lost, neurons die and the brain shrinks, especially in the hippocampus, the brain's memory center.

Researchers now recognize that plaques and tangles are only part of the story. Chronic neuroinflammation driven by overactive immune cells in the brain called microglia, reduced blood flow, damage to small blood vessels, oxidative stress and mitochondrial dysfunction all contribute to the disease process.

Currently, we can distinguish two main forms of AD. Early-onset familial AD is rare, typically appears before age 65, and is caused by inherited mutations in one of three genes: APP, PSEN1 or PSEN2. Late-onset sporadic AD accounts for the vast majority of cases and results from a combination of age, genetics, lifestyle and environment. The strongest genetic risk factor for late-onset AD is the APOE4 gene variant. Carrying one or two copies increases risk but does not guarantee the disease will develop.

Traditional Treatments

For many years, AD medications have focused on symptoms. Cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine can help with memory and thinking for a period of time, but they do not stop the underlying disease from progressing.

More recently, the FDA approved anti-amyloid antibody infusions, lecanemab (Leqembi) and donanemab (Kisunla), for people with early AD. These drugs clear amyloid plaques from the brain and modestly slow decline. In the lecanemab phase 3 trial, decline on a standard dementia rating scale was about 27% slower than with placebo over 18 months. However, these therapies require regular infusions and MRI monitoring, are approved only for early-

stage disease, and carry a risk of brain swelling and microbleeds known as ARIA (amyloid-related imaging abnormalities), particularly in people who carry the APOE4 gene.

Lifestyle measures, including physical exercise, cognitive and social engagement, good sleep, and management of blood pressure, diabetes and hearing loss, remain important for brain health. Still, there is a major need for therapies that address the inflammation and tissue damage driving AD.

Stem Cell Therapy for Alzheimer's Disease

Mesenchymal stem cells (MSCs) are adult stem cells found in umbilical cord tissue, bone marrow and fat. Rather than replacing lost neurons, MSCs act as “medicinal signaling cells,” releasing growth factors, anti-inflammatory molecules and exosomes that help calm inflammation, support blood vessels and protect existing brain cells.

Animal studies have been very encouraging. A 2025 meta-analysis pooled 13 studies of umbilical cord MSCs in Alzheimer's mouse models. Treated animals showed significantly better learning and memory, lower beta-amyloid levels in the brain, higher levels of brain-derived neurotrophic factor (BDNF) and less nerve cell death.

Researchers have also studied the intranasal route, which allows biologics to travel from the nose to the brain along the olfactory and trigeminal nerves. In a mouse model of AD, intranasal MSC exosomes calmed overactive microglia and increased the density of dendritic spines, the tiny connection points between neurons. In aged AD mice, once-weekly intranasal delivery of factors secreted by MSCs produced lasting memory recovery and a marked reduction in amyloid plaques.

In 2025, Nature Medicine published the CLEAR MIND trial, a randomized, double-blind, placebo-controlled

phase 2a study of donor bone marrow MSCs (Iaromestrocel) given intravenously to 49 people with mild AD. Over 39 weeks, patients who received the cells had about 48% slower whole-brain shrinkage and 59% slower shrinkage of the hippocampus than those on placebo. The treated group also showed improvement on the Montreal Cognitive Assessment (MoCA) and on measures of daily living and quality of life. The cells were well tolerated, and an earlier phase 1 study of the same product found no ARIA-type brain swelling, including in APOE4 carriers. The FDA has granted this therapy Regenerative Medicine Advanced Therapy (RMAT) and Fast Track designations, and a phase 3 trial is being planned. As the authors note, larger trials are needed to confirm the cognitive benefits.

In 2023, researchers in China published the first clinical trial of intranasal MSC-derived exosomes in AD. Patients with mild to moderate AD received donor adipose MSC exosomes intranasally twice a week for 12 weeks. No adverse events were reported, and in the medium-dose group, memory and thinking scores improved at 12 weeks compared with baseline, with less hippocampal shrinkage. The study was small and had no placebo group, so these results are encouraging but early.

A Korean phase 2a trial published in 2025 delivered umbilical cord blood MSCs directly into the fluid spaces of the brain through a surgically implanted reservoir. The cells lowered amyloid and tau markers in spinal fluid compared with placebo, although differences in cognition were not significant, and patients had more temporary fever and headache. This route is far more invasive than intravenous or intranasal delivery.

A 2025 review of MSC clinical trials in AD concluded that MSC therapy is feasible and generally safe, with signs of benefit in cognition and quality of life in some patients, while noting that larger trials are still needed to confirm effectiveness.

Stem cells and exosomes act in the body through several mechanisms. They do NOT become part of a patient's DNA, and they are not expected to permanently engraft or turn into new brain cells.

They act through:

1. Reducing neuroinflammation – AD is driven in part by chronic inflammation from

4. Cellular signaling – Through “cell to cell” communication, the biologics deliver proteins and genetic messages (mRNA and microRNA)

overactive microglia. MSCs and exosomes help shift microglia from a damaging state toward a protective, repair-oriented state.

2. Immune system modulation – Instead of blanketly suppressing the immune system like steroids, regenerative biologics tamp down harmful inflammatory signals while boosting helpful growth factors and anti-inflammatory cytokines.

3. Supporting blood flow – Reduced blood flow and damage to small vessels contribute to AD. MSCs release factors such as VEGF that support blood vessel health and the formation of new vessels (angiogenesis).

that prompt the brain's own cells to produce protective growth factors such as BDNF.

5. Protecting neurons – Regenerative biologics help shield stressed neurons from programmed cell death (apoptosis) and support the synapses that connect them.

6. Helping clear toxic proteins – In laboratory and animal studies, MSCs and their exosomes enhanced the clearance of beta-amyloid, in part by activating the natural clean-up function of microglia.

Table 1. Proteins involved in the therapeutic mechanisms of MSCs in Alzheimer's disease (summarized from preclinical research).

Therapeutic Benefits	Proteins	Mechanisms
Attenuate neuroinflammation	IL-1 β , TNF- α , IFN- γ	Decreased pro-inflammatory cytokines that drive microglial activation
	IL-10, TGF- β	Increased anti-inflammatory cytokines
	PGE2, TSG-6	Shift microglia toward a protective phenotype
Release neurotrophic factors	BDNF	Supports neuron survival, synaptic plasticity and memory
	NGF	Supports cholinergic neurons involved in memory
	GDNF	Protects neurons from stress-induced death
Support vascular health	VEGF, Ang-1	Promote angiogenesis and blood vessel stability
Promote amyloid clearance	Neprilysin	Amyloid-degrading enzyme carried by MSC exosomes
	CCL5	Recruits microglia that help clear amyloid plaques
Protect neurons and synapses	Anti-apoptotic microRNAs	Reduce neuronal apoptosis and support synapse integrity

Stem cells also release a huge variety of molecules into the extracellular environment. These molecules, which include extracellular vesicles (exosomes), lipids, free nucleic acids and soluble proteins, play crucial roles in repairing damaged tissue. Along with offering stem cells for treatment of AD, R3 Stem Cell includes stem cell exosomes, a type of extracellular vesicle that participates in extensive cell-to-cell communication for central nervous system repair and regeneration.

The stem cells administered by R3 are not the ones that become a patient's new neurons. The administered mesenchymal stem cells are not designed to replace lost brain cells, but rather to coordinate and enhance a repair response by the body's own mechanisms.

Where do the stem cells and exosomes come from?

R3 Stem Cell's regenerative biologics originate from umbilical cord tissue that has been donated after a scheduled c-section. No baby (or mother) is harmed during the c-section procedure. The umbilical cord tissue is normally discarded, but if the mother passes screening tests, the umbilical cord is immediately sent to the lab.

The lab carefully processes the umbilical cord to generate large amounts of stem cells and exosomes of the highest possible quality. The lab team consists of multiple PhDs working in ISO-certified, cGMP-compliant clean rooms. The proprietary production process combines potency, safety and affordability so providers can confidently offer stem cell and exosome procedures.

Millions of dollars have been invested in pharmaceutical-grade production of the biologics, including first-rate clean rooms, bioreactors, nanoparticle tracking analyzers, cytometers, PCR, tangential flow machines and real-time environmental monitoring. Quality assurance testing complies with screening and testing standards consistent with the American Association of Tissue Banks, cGMP standards and FDA regulations.

Stem Cell Derived Exosomes

R3 Stem Cell's Centers of Excellence globally include umbilical cord stem cell derived exosomes with umbilical cord stem cells. Exosomes are lipid-bound vesicles (acellular) produced by cells, and they

contain a plethora of growth factors, cytokines, mRNA, microRNA and other proteins.

Exosomes are exceptionally helpful in cell-to-cell communication and are very effective at reducing inflammation once they are taken up by their recipient cells. They act as shuttles that carry nucleic acids and proteins to other cells, allowing communication among both nearby and distant cells.

Exosomes are believed to mediate many of the therapeutic effects of stem cells. Because they are roughly 100 times smaller than stem cells, they can reach places that cells cannot. In animal studies, exosomes given intranasally travel directly from the nose to the brain, which is why intranasal delivery is a major focus of Alzheimer's research.

Is stem cell therapy safe?

After a decade of performing over 30,000 stem cell procedures worldwide, R3 has extensive experience with the safety of regenerative procedures. The quality control employed during stem cell production is second to none, and the side effects R3 sees are usually mild to moderate and temporary.

They may include itching, dizziness, lightheadedness, low-grade fever, chills, headache and nausea. These are typically temporary. If a patient has an allergic reaction to the multivitamin or a preservative, all of R3's Centers have the medications to resolve it quickly.

One of the questions we get asked a lot is, "Will the stem cells get rejected?" Rejection is very unlikely. MSCs do not express major histocompatibility complex (MHC) class II antigens and express only low levels of MHC class I molecules. MSCs also lack the co-stimulatory molecules essential for immune detection, including CD40, CD80 and CD86. As a result, MSCs have low immunogenicity, which is why they can be used without matching the donor to the recipient.

Another question often asked is, "Is there a chance of a tumor forming?" Unlike embryonic stem cells, MSCs do not have tumor-forming (teratoma) potential, and MSCs and exosomes have not been shown to cause tumors in clinical trials to date.

For Alzheimer's patients, a common safety question involves ARIA, the brain swelling and microbleeds seen with anti-amyloid drugs. In the phase 1 study of

donor MSCs for AD, no ARIA was observed, including in APOE4 carriers.

Treatment Protocol

For the past decade, R3 has treated patients with stem cell and exosome therapies through injection, infusion, intranasal, intrathecal and nebulizer routes. For Alzheimer's disease, treatment is individualized. Oftentimes, a combination of intravenous, intrathecal and intranasal delivery is used. Intranasal delivery takes advantage of the direct nose-to-brain pathway studied in Alzheimer's research, while intrathecal application avoids the blood-brain-barrier altogether. Intravenous delivery addresses the body-wide inflammation and vascular factors linked to AD.

For AD, R3's providers use between one and three million stem cells per kilogram. In addition, billions of stem cell exosomes are included. Safety is paramount, with the biologics rigorously tested prior to use and expert providers managing each treatment as if you were a family member!

Because AD is a progressive disease, families should expect gradual changes rather than an overnight transformation, and most patients will need repeat treatments every one to two years. R3 tracks patient outcomes through its IRB-approved observational safety database, so results can be measured over time.

Why does R3 Stem Cell use donor tissue for its stem cells?

Although autologous (your own) stem cells offer some advantages, allogeneic (donor) stem cells have more. First, autologous MSCs need a long time to culture and expand, which delays treatment, while allogeneic stem cells can be obtained and expanded more quickly.

Second, age affects the characteristics of MSCs. Studies have shown that stem cells from elderly donors have decreased proliferation and differentiation ability, meaning they are fewer in number and less effective. This matters especially for Alzheimer's, since most patients are over 65 and their own stem cells would be older and less active.

Affordability

Stem cell therapy for AD may help support brain health and quality of life, and we want to make it affordable for as many families as possible. Our

global volume has allowed us to keep patient costs as low as possible. Since most patients will need repeat therapies, treatment cost is extremely important.

Unfortunately, stem cell clinics in Colombia, China and Panama charge over \$30,000 USD for treatment of neurological conditions. How are families supposed to budget for that? R3 Stem Cell's fees are typically less than half that for full treatment, which also includes free exosomes and a multivitamin infusion!

R3's Experience

For the past decade, R3 Stem Cell's Centers globally have performed over 30,000 regenerative procedures in eight countries. Patient satisfaction across all conditions treated is very high, at 85%. However, MSC treatment for AD is a MUCH newer option, so satisfaction percentages haven't been definitively established.

R3 combines safety, effectiveness and affordability. Internationally, the Intellicell is used, culturing the most active mesenchymal stem cells to create the "smartest" stem cell in the world!

R3 Stem Cell offers free consultations to discuss whether regenerative therapy is indicated for your loved one's Alzheimer's disease. Simply call **+1 (844) GET-STEM** to schedule yours.

References:

1. Rash BG, et al. Allogeneic mesenchymal stem cell therapy with laromestrol in mild Alzheimer's disease: a randomized controlled phase 2a trial. *Nat Med.* 2025;31(4):1257–1266.
2. Xie X, et al. Clinical safety and efficacy of allogenic human adipose mesenchymal stromal cells-derived exosomes in patients with mild to moderate Alzheimer's disease: a phase I/II clinical trial. *Gen Psychiatr.* 2023;36(5):e101143.
3. Lee NK, Jang H, Choi Y, et al. Mesenchymal stem cells with adjuvant dexamethasone in patients with Alzheimer's disease: a phase IIa trial. *Dement Neurocogn Disord.* 2025;24(4):272–285.
4. Kim HJ, Cho KR, Jang H, 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;13:154.
5. Human umbilical cord mesenchymal stem cells therapy for Alzheimer's disease: a systematic review and meta-analysis of mouse models. 2026. PMID: 41847685.
6. Losurdo M, et al. Intranasal delivery of mesenchymal stem cell-derived extracellular vesicles exerts immunomodulatory and neuroprotective effects in a 3xTg model of Alzheimer's disease. *Stem Cells Transl Med.* 2020;9(9):1068–1084.
7. Santamaria G, et al. Intranasal delivery of mesenchymal stem cell secretome repairs the brain of Alzheimer's mice. *Cell Death Differ.* 2021;28:203–218. doi:10.1038/s41418-020-0592-2.
8. Therapeutic efficacy of mesenchymal stem cells (MSCs) on Alzheimer's disease: review of clinical results. *Tissue Eng Regen Med.* 2025. doi:10.1007/s13770-025-00762-1.
9. van Dyck CH, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med.* 2023;388:9–21.

About R3 Stem Cell

David Greene, MD, PhD, MBA, Founder/CEO



R3 Stem Cell offers treatments that bring patients and families hope and options. Hope that quality of life can be improved, and that the body's own repair mechanisms can be supported so patients can get back to the activities and people they love.

Founder and CEO David Greene, MD, PhD, MBA writes extensively on regenerative medicine, is the author of Stem Cell Genius: Your Front Row Seat to the Future of Regenerative Medicine, and gives seminars worldwide on a regular basis. With over 80 Centers of Excellence globally, R3 is at the forefront of regenerative therapies.

R3's Centers have successfully performed over 30,000 regenerative procedures to date. Call today for your free consultation **(844) GET-STEM!**

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