MedCrave
Step into the World of Research

Journal of Stem Cell Research & Therapeutics

Research Article

Open Access

CrossMark

# Stem cell use in treating Parkinson's disease

## Abstract

Parkinson's disease is a progressive neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra, leading to reduced dopamine transmission to the putamen and resulting in both motor and non-motor symptoms. Current treatments include dopaminergic medications, enzyme inhibitors, deep brain stimulation, and rehabilitative therapies that can help manage symptoms but do not prevent ongoing neurodegeneration. Due to this limitation regarding treatment, there is growing interest in regenerative approaches that may restore dopaminergic function. This research paper examines mesenchymal stem cells, human embryonic stem cells, and induced pluripotent stem cells as emerging treatments for Parkinson's disease, integrating both preclinical evidence and clinical trial findings. Across studies, mesenchymal stem cells whether autologous or allogeneic, demonstrate safety, feasibility, and early biological activity, including reductions in inflammation and improvements in motor symptoms. Trials involving human embryonic stem cell-derived dopaminergic progenitors show dopaminergic neuron progenitor survival, increased dopamine synthesis on PET imaging, and dose-dependent improvements in motor function. Induced pluripotent stem cell-based approaches, both autologous and allogeneic, also demonstrate safety and biological activity, with PET imaging confirming dopaminergic function of transplanted cells. Overall, current evidence suggests that stem-cell–based therapies may offer promising disease-improving effects, supporting the need for larger and more controlled clinical studies.

**Keywords:** Parkinson's disease, mesenchymal stem cells, human embryonic stem cells, induced pluripotent stem cells, regenerative medicine, clinical trials

Volume 11 Issue 1 - 2026

Breanna Wickham, Vincent S Gallicchio
Department of Biological Sciences, College of Science, Clemson University, USA

**Correspondence:** Dr. Vincent S. Gallicchio, Department of Biological Sciences, 122 Long Hall, College of Science Clemson University, Clemson, SC 29627, USA

**Received:** January 16, 2026 | **Published:** February 16, 2026

**Abbreviations:** 6-OHDA, 6-hydroxydopamine; BDNF, brain derived neurotropic factor; BM-MSCs, bone marrow derived mesenchymal stem cells; COMT, catechol O-methyltransferase; DA, dopamine; hESCs, human embryonic stem cells; H&Y, hoehn and yahr; iPSCs, induced pluripotent embryonic stem cells; L-DOPA, levodopa; MAO-B, monoamine oxidase B; MDS-UPDRS, movement disorder society-sponsored unified parkinson's disease rating scale; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSC, mesenchymal stem cells; PD, Parkinson's disease; SVZ, subventricular zone; UPDRS; unified parkinson's disease rating scale

## Introduction

### Pathophysiology of PD

PD is a chronic, progressive, neurodegenerative disease that most notably affects an individual's ability to have smooth, controlled movements. These symptoms are caused by a decrease in the production of DA, a neurotransmitter essential for fine-tuning movement.[1] Overall, movement control is created by interactions among many groups of nerve cells in the central nervous system.[2] A group of neurons in the central nervous system that are especiallyimportant for movement control are the ones in the substantia nigra, a region present in the ventral midbrain. In the substantia nigra, neurons produce DA and transmit it to the neurons in the basal ganglia, particularly the area in the basal ganglia called the corpus striatum. This DA is synthesized within substantia nigra neurons through the enzymatic conversion of the amino acid tyrosine into the amino acid L-DOPA by tyrosine hydroxylase, followed by its conversion into DA by aromatic L-amino acid decarboxylase (AADC).[3] The production and communication of DA are responsible for fine-tuned movement.[2] However, in PD, the neurons in the substantia nigra that produce DA degenerate due to the presence of abnormal protein accumulations called Lewy bodies. Lewy bodies are formed when the protein alpha-synuclein misfolds and clumps together inside brain cells.[4] These Lewy bodies are associated with neuron dysfunction and degeneration, which reduces DA production.[5] However, the exact relationship between Lewy bodies and neuron death is not fully understood, and it remains an active area of research.[4] In addition, higher levels of inflammatory markers can harm DA-producing neurons and degrade them by creating oxidative stress and damaging their normal function.[6] Lower levels of BDNF, a protein that helps keep neurons healthy, also make these neurons more likely to die.[7] With less BDNF, the neurons in the substantia nigra have less support to survive everyday stress and injury.[8] Thus, the presence of Lewy bodies, increases in inflammatory markers, and decreases in BDNF contributes to neuronal dysfunction and degeneration, which reduces DA production and decreases the amount of DA reaching the basal ganglia.[2,3,6-8] Specifically, the area in the corpus striatum known as the putamen is most severely affected by this disease, as it is the primary target of DA release from the substantia nigra and is very essential in the control of motor function.[9] This lack of DA, particularly the lack of it communicated with the putamen, manifests as clinical symptoms such as tremors beginning in the hands or fingers, slowed movements, poor posture, balance issues, changes in speech, and rigid muscles (Figure 1).[1]

### Current treatment options for Parkinson's patients

PD is not curable with currently available treatment. However, there are FDA-approved treatments that can help alleviate symptoms of the disease. The main types of treatment include medications, surgery, and therapy. Regarding medications, some of these include DA agonists, DA precursors, and inhibitors that block the enzymes that degrade DA, such as MAO-Band COMT. DA agonists mimic the action of DA by directly stimulating DA receptors in the brain, helping improve motor symptoms even when natural DA levels are low. DA precursors, such as L-DOPA, are converted into DA within the brain to create new DA. MAO-B and COMT inhibitors prevent the breakdown of DA by blocking the enzymes that degrade it, thereby allowing DA to remain active for a longer period. Another method

of treatment for PD is surgical methods. One of the primary surgical methods is deep-brain stimulation (DBS). Deep brain stimulation involves placing electrodes within the brain, which are connected to a generator that sends electrical signals to the brain, thereby helping to reduce symptoms of PD. As well as medications and surgery, therapy is also a treatment option for those with PD. Some of these include physical therapy (to improve mobility, balance, and muscle strength), occupational therapy (to make daily activities safer and easier), and speech therapy (to enhance speech clarity, voice volume, and swallowing function).[1] However, there are limitations to these treatments, including their provision of only symptomatic care and the decline in benefits over time.[10] There is a need for treatments that utilize regenerative approaches to restore dopaminergic function.

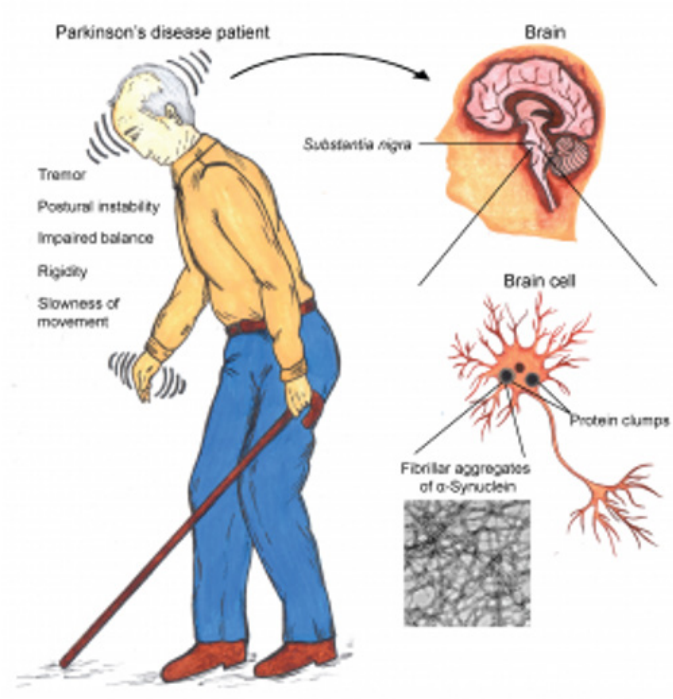


**Figure 1** The pathophysiology of Parkinson's disease.[10]

## Side effects of current treatment for Parkinson's patients

In addition to the symptoms caused by the progression of PD itself, individuals may also experience side effects resulting from treatment, particularly from long-term dopaminergic medication therapy. Medications such as L-DOPA, DA agonists, and MAO-B or COMT inhibitors can lead to complications including dyskinesias (slow movement), motor fluctuations, and worsening bradykinesia during "OFF" periods when medication is not taken. These motor complications occur because, as neurodegeneration continues, the brain becomes more dependent on external DA replacement and more sensitive to changes in drug delivery.[11] Thus, the occurrence of worsening motor symptoms as a side effect of these treatments highlights the need for regenerative treatments capable of restoring or replacing lost dopaminergic neurons rather than relying solely on symptomatic management in patients with PD.

## Idiopathic vs atypical PD

Regarding PD, there are different presentations of it. Idiopathic PD is the classic form of Parkinson's. Meaning that idiopathic PD is a progressive neurodegenerative disorder caused primarily by loss of dopaminergic neurons, leading to hallmark symptoms about movement. In contrast, Parkinson-plus also produces the hallmark symptoms regarding movement but also additional symptoms that are not typical of idiopathic Parkinson's. These may include abnormal eye movements, "drunken" gait, abnormal postures, problems with blood pressure regulation after standing, unusual changes in reflexes, and cognitive decline among others. Due to these additional symptoms, and because these disorders often respond poorly to standard Parkinson's medications, Parkinson-plus syndromes tend to be more aggressive and harder to treat than idiopathic Parkinson's (Figure 2).[12]

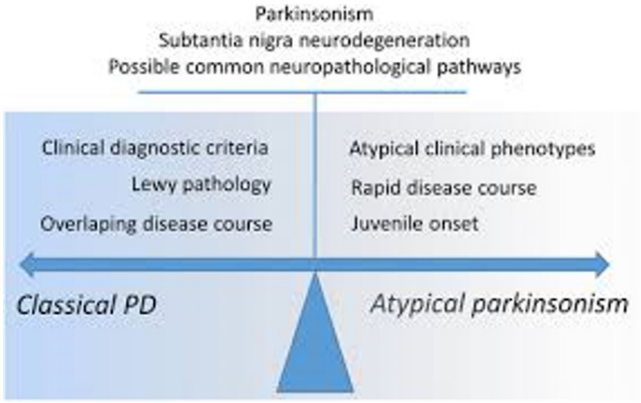


**Figure 2** Classic/idiopathic and atypical/Parkinson's plus PD.[14]

## Databases and search strategies

A literature search was conducted in PubMed to identify clinical trials evaluating stem cell therapies for Parkinson disease. Medical Subject Headings (MeSH) and keywords, including "Parkinson Disease," "Stem Cells," "Cell Transplantation," and "Dopaminergic Neurons," were combined using Boolean operators.

# Discussion

## Stem cells as potential therapeutic approaches in PD

Stem-cell-based therapy for PD represents one of the most promising areas in the future treatment of this disease, as it offers the possibility of protecting, replacing, or regenerating dopaminergic neuron cells that are lost to the disease. Thus, protecting, replacing, or regenerating these dopaminergic neurons provides the possibility of restoring DA in the brain and helping to alleviate the symptoms caused by this lack of DA.[13] MSCs, hESCs, and iPSCs are prominent types of stem cells that have been used in clinical trials to explore their potential for treating PD. Overall, these clinical trials have demonstrated positive outcomes for patients with PD, including increased DA levels and a reduction in tumors on neuroimaging, as well as improved performance on clinical tests. However, there are currently no FDA-approved stem cell treatments for PD.

## Common methodology in stem cell treatment for PD clinical trials

Throughout clinical trials investigating stem cell–based interventions for PD, standard methodologies for assessing both dopaminergic changes and corresponding clinical outcomes rely on a combination of neuroimaging techniques and clinical rating scales.

Among these clinical rating scales, H&Y staging, the MDS-UPDRSParts I–IV, and the original UPDRSare most used. These clinical rating scales are used during screening and baseline evaluation as well as periodically throughout follow-up to monitor changes

**Citation:** Wickham B, Gallicchio VS. Stem cell use in treating Parkinson's disease. *J Stem Cell Res Ther.* 2026;11(1):25–36.
DOI: 10.15406/jsrt.2026.11.00216

in symptom severity. The H&Y scale is a global staging system that ranges from 0 (no signs of disease) to 5 (wheelchair-bound or bedridden unless assisted), primarily evaluating motor impairment, balance, gait, and functional independence.[14] The MDS-UPDRS parts I-IV provide a more detailed assessment. Part I evaluates non-motor symptoms, including sleep disturbances, mood, autonomic changes, and cognition. Part II assesses activities of daily living. Part III evaluates the core motor features of PD, including tremor, rigidity, bradykinesia, posture, gait, and facial expression. Part IV evaluates problems caused by long-term Parkinson's medications, such as involuntary movements, changes in how well the medication works throughout the day, and painful muscle tightening when the medication wears off. Parts I and II each contain 13 items scored 0–4, for a maximum score of 52. Part III contains 33 motor items scored 0–4, for a maximum score of 132. Parts I and II are typically not influenced by medication. However, Part III is often administered in both ON-medication (with typical PD–treating medications, such as L-DOPA) and OFF-medication (without typical PD–treating medications) conditions to evaluate changes in scores as a function of whether the patient is taking medication. Part IV contains 6 items scored 0–4. Overall, this section has a maximum total score of 24 and evaluates the impact of long-term typical dopaminergic therapy on daily functioning. Overall, a higher score in this rating scale indicates higher disease severity.[15]

Before the development of the MDS-UPDRS, early stem cell trials used the original UPDRS as the principal clinical assessment tool.[16] This scale evaluates PD severity across four sections. Part I covers mentation, behavior, and mood and consists of 4 items. Part II covers activities of daily living and consists of 13 items. Part III covers motor examinations and consists of 28 items. Part IV covers therapy complications and consists of 11 items. Each item is scored from 0 (normal) to 4 (severe impairment), yielding a total possible score ranging from 0 to 147. In this scale, higher scores reflect greater disability. Like the MDS-UPDRS Part III, the original UPDRS was commonly administered in both ON and OFF medication states to evaluate disease severity with and without typical PD-treating medication.[17]

## MSC treatment of PD

MSCs are multipotent cells found in various tissues, including menstrual blood, the umbilical cord, bone marrow, adipose tissue, and endometrium, among others and some that have yet to be discovered. Overall, this type of stem cell is beneficial for clinical applications.[18] The advantages of using MSCs in clinical applications, such as stem cell therapy, include their easy attainability from various tissue sources within the body through a simple procedure and their ability to be produced on a large scale. However, there are disadvantages to utilizing MSCs in therapeutic applications. The first disadvantage is the replicative senescence of these cells caused by telomere shortening and lack of telomerase activity. Overall, this restricts their expansion for therapeutic use unless corrected by the expression of the hTERT (human telomerase reverse transcriptase gene). Another disadvantage of MSCs is that they carry a potential risk for cancer. They carry this risk for cancer because keeping these cells in long-term culture can cause stress and repeated cell division, which increases the chance of genetic changes and chromosome instability. Their immune-suppressing and cytokine-releasing effects could also accidentally help tumors grow.[19] Despite the disadvantages associated with them, MSCs are of significant use in clinical research, including clinical trials that test MSCs as a treatment for PD. Primarily, these studies utilize autologous or allogeneic BM-MSCs to provide neuroprotective and anti-inflammatory effects in the brain, releasing growth factors, reducing inflammation, and supporting the survival of remaining dopaminergic neurons.[20,21] MSCs do not reliably transform into dopaminergic neurons in humans. Instead, these stem cells act through paracrine signaling, modulating the brain environment to promote repair and improve neuronal function (Figure 3).[22,23]

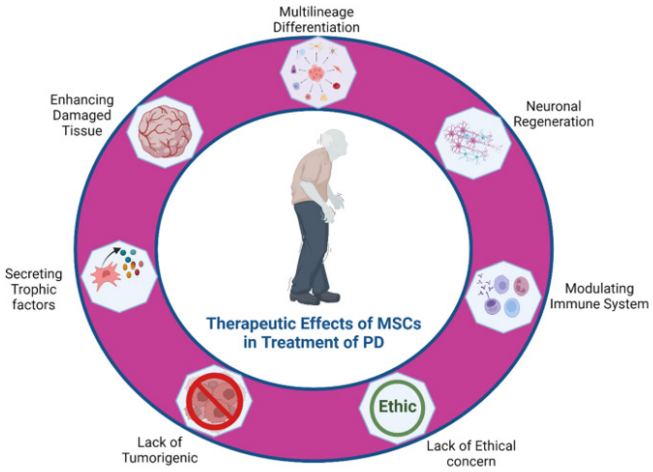


**Figure 3** Therapeutic effects of MSCs in treatment of PD.[26]

## Autologous BM-MSC treatment of PD

Autologous BM-MSCs represent one of the earliest stem-cell–based strategies explored in clinical trials for PD.[24,25] These cells are obtained directly from the patient's own bone marrow. So, using these stem cells eliminates the risk of immune rejection. Additionally, they do not require immunosuppressive medications. After these BM-MSCs are obtained from the patient, they are expanded in vitro to get a therapeutic dose. From there, they are transplanted back into the same patient.[25]

Two early clinical trials investigated the safety and feasibility of using this variety of MSCs in treating patients with PD.[24,25] An early study was conducted in India, where autologous BM-MSCs were directly delivered into the putamen using stereotactic MRI-guided neurosurgery.[24] A later study, performed in Belarus, evaluated the less invasive delivery of autologous BM-MSCs. This method of delivery involved both intravenous infusion and combined intranasal and intravenous administration. These trials were conducted in India and Belarus.[24,25]

## Preclinical evidence

A key preclinical study supporting the use of autologous bone-marrow-derived MSCs for PD showed that transplantation of each rat's own BM-MSCs into the substantia nigra of 6-OHDA (a neurotoxin destroying dopaminergic neurons) treated rats significantly improved motor behavior, increased survival of dopaminergic neurons, and reduced local inflammation. Thus, demonstrating neuroprotective and anti-inflammatory effects of autologous BM-MSCs on dopaminergic neurons in rats.[26] Another important study found that autologous BM-MSCs transplanted into the striatum of 6-OHDA treated rats boosted neurotrophic factor levels such as BDNF, supported partial restoration of dopaminergic neurons, and improved motor symptoms. These results suggest that autologous bone-marrow can help recover dopaminergic function in rats.[27] Overall, these studies show that autologous BM-MSCs can be safely administered and can improve dopaminergic neuron survival and motor outcomes in rodent PD models.[26,27] Thus, providing a solid basis for translation into human autologous BM-MSC clinical trials for treating PD.

**Citation:** Wickham B, Gallicchio VS. Stem cell use in treating Parkinson's disease. *J Stem Cell Res Ther.* 2026;11(1):25–36.
DOI: 10.15406/jsrt.2026.11.00216

## Clinical trial 1: unilateral autologous BM-MSC transplantation

This early open-label pilot study, conducted in India for 36 months and completed in 2010 evaluated the safety and feasibility of unilateral autologous BM-MSC transplantation in patients with moderate to advanced PD. It was one of the earliest clinical studies to test the safety of autologous BM-MSC therapy in PD. Seven participants received stereotactic unilateral implantation of autologous BM-MSCs into the SVZ using MRI guidance. In this early clinical trial, autologous BM-MSCs were obtained by aspirating 60 mL of bone marrow from each patient's iliac crest and isolating the mononuclear cells. From there, the mononuclear cells were expanded in vitro before transplantation. The final product was delivered as a single stereotactic dose of MSCs implanted into the SVZ.[24] The SVZ is a natural stem-cell region in the brain. Here, new neurons are produced that then migrate to the basal ganglia.[28] Placing MSCs there allows them to act in an environment already geared toward repair, potentially strengthening their supportive and neuroprotective effects. In addition to using MRI to guide the implantation of BM-MSCs, MRI was also employed post-implantation to detect potential structural abnormalities, such as tumors.[24]

Clinical assessments completed after implantation included the UPDRS rating scale and H&Y staging.[24] These clinical rating scales were used to assess the severity of non-motor symptoms, the ability to perform activities of daily living, the severity of motor symptoms, and complications arising from standard therapy for PD.

In this study, researchers observed no adverse events following implantation of BM-MSCs. Overall, this treatment is shown to be both safe and feasible. In addition to this study demonstrating the safety of this treatment, some improvements in motor symptoms and disease stage were also observed following the transplantation of autologous BM-MSCs. Before treatment, the average UPDRS score was 65 in the OFF-medication state and 50.6 in the ON-medication state. Among the three out of the seven patients who showed consistent improvement, OFF-state scores decreased to 43.3, and ON-state scores decreased to 31.7 by the final follow-up of the study. Regarding H&Y staging, some improvements in disease severity were also noted. The average baseline stage was 2.7, and several patients moved to a lower stage during follow-up. Overall, this demonstrates better balance, gait, and overall motor function. However, responses to this treatment varied among participants, and not all patients experienced the same degree of benefit.[24]

Overall, the results showed possible symptomatic improvements in a subset of patients. However, the lack of a control group and small sample size limit the strength of the conclusions. This study mainly served as a feasibility and safety study rather than a study to determine the efficacy of this treatment. However, it helped to justify more structured and larger studies using autologous BM-MSCs in the treatment of PD.[24]

## Clinical trial 2: autologous BM-MSC IV vs intranasal+IV

Another clinical trial investigating the treatment of BM-MSCs for PD was conducted in Belarus in 2019 for 3 months. This study was more structured than the one completed in India in 2010 and investigated the delivery of these stem cells either intravenously alone or via a combination of intranasal and intravenous administration in patients with PD. In this trial, 12 patients with PD received BM-MSC treatment and were compared with 11 control participants who received standard medical therapy for PD. For the twelve patients with PD, bone marrow was aspirated from the posterior iliac crest. The mononuclear cells present in the bone marrow were then isolated and expanded in vitro to generate autologous BM-MSCs. Then, these cells were administered via two possible routes: systemic intravenous infusion or "tandem" intranasal administration, in addition to intravenous injection. The systemic intravenous infusion route involved 0.5 to 2.0 million cells/kg given in three weekly infusions. The "tandem" route involved injecting 5.0 to 12.6 million cells into the olfactory mucosa, and 7 days later, 10–50 million cells were administered intravenously in two infusions, one week apart. After transplantation, follow-up visits were conducted at one- and three-months post-implantation.[25]

In this clinical trial, several standardized clinical rating methods were used to track both motor and non-motor symptoms following administration of autologous BM-MSCs. Motor symptom severity was measured using the MDS-UPDRS Part III. This clinical rating scale was assessed in both the medication-OFF state (after 12–24 hours without dopaminergic medication) and the ON state (one hour after medication administration). Non-motor symptoms were evaluated using other scales as opposed to MDS-UPDRS Parts I-II. These included the Hamilton Depression Rating Scale (HDRS) for mood, the Pittsburgh Sleep Quality Index (PSQI) for sleep quality at night, the Epworth Sleepiness Scale (ESS) for sleepiness during the day, the Non-Motor Symptoms Scale (NMS) for non-motor symptoms, and the PDQ-39 Summary Index for quality of life. Disease severity was assessed using the H&Y staging system, which provides a baseline measure of disease severity. Neuroimaging in this study was limited to routine MRI used for screening and safety evaluation.[25]

In this study, researchers reported no adverse events, including infections, allergic reactions, or tumor formation. Overall, this treatment is shown to be safe and feasible. The results reflected improvements across several domains, particularly in the group receiving MSC transplantation as opposed to standard medical therapy for PD. MDS-UPDRS Part III OFF-state motor scores improved from a baseline median of about 36.5 to 33.5 at one month and 32.0 at three months. Overall, this represents a meaningful reduction in motor symptom severity. In comparison, MDS-UPDRS Part III ON-state scores remained essentially unchanged throughout the study. Mood improved substantially with HDRS scores decreasing from approximately 12.5 to 8.0 and then 7.0 over the 3-month follow-up. Sleep measures also showed benefits. PSQI scores modestly improved, and ESS daytime sleepiness scores declined from approximately 12 to 7, indicating less severe daytime drowsiness. NMS total scores showed a slight improvement trend but did not reach statistical significance within the short study duration of 3 months. Quality of life also improved, with PDQ-39 Summary Index scores decreasing from approximately 45.5 to around 32. The H&Y staging remained stable, with no significant shift over the three months. It is also important to note that the study did not explicitly report any differences in clinical outcomes between the two routes of administration of autologous BM-MSCs.[25]

Overall, the findings from this trial demonstrated the safety of autologous BM-MSCs as a treatment for PD. In addition to safety, this study's results also include improvements in motor, mood, sleep, and quality-of-life measures in patients receiving autologous BM-MSCs. However, the small sample size and short follow-up period limit the strength of the conclusions. Nonetheless, the proven safety of these stem cells in treating Parkinson's provides additional justification, along with the 2010 study in India, for pursuing more advanced and efficacy-based studies of autologous MSC therapy in PD.[24,25]

**Citation:** Wickham B, Gallicchio VS. Stem cell use in treating Parkinson's disease. *J Stem Cell Res Ther.* 2026;11(1):25–36.
DOI: 10.15406/jsrt.2026.11.00216

## Clinical trials involving autologous BM-MSC treatment of PD

Across two major clinical trials investigating autologous BM-MSCs for PD, several similarities and differences emerge regarding study design, delivery methods, and clinical outcomes.[24,25] Foundational preclinical studies demonstrated that autologous MSCs can exert strong neuroprotective and anti-inflammatory effects in rodent models of PD.[26,27] A key preclinical study showed that transplantation of each rat's own BM-MSCs into the substantia nigra of 6-OHDA-treated rats significantly improved motor behavior and demonstrated protective effects of autologous BM-MSCs on dopaminergic neurons.[26] Another important study found that autologous BM-MSCs transplanted into the striatum of 6-OHDA-treated rats helped to recover dopaminergic function.[27] Overall, these studies show that autologous MSCs can be safely administered and can improve dopaminergic neuron survival and motor outcomes in rodent PD models, providing a solid basis for translation into early human autologous MSC trials.[26,27]

One of the earliest clinical studies, conducted in India, used a neurosurgical approach in which autologous BM-MSCs were stereotactically implanted into the SVZ, a natural stem-cell area. This study primarily served as a feasibility and safety trial, utilizing a single dose and focusing mainly on motor symptom changes through UPDRS and H&Y staging.[24] In contrast, the later trial conducted in Belarus had a more structured design, incorporated a control group, and used systemic infusion-based delivery, with some participants also receiving intranasal administration. This study had substantially higher and more variable doses than the 2010 trial and incorporated a larger range of clinical assessments including mood, sleep quality, daytime alertness, and quality-of-life measures in addition to MDS-UPDRS motor symptom testing.[25]

Despite these differences in methods among these two clinical trials, both studies demonstrated that autologous bone-marrow derived MSC therapy is safe and well tolerated with no reports of tumor formation, or reactions.[24,25] However, consistency of clinical improvement in these clinical trials varied. In the 2010 SVZ implantation study, improvements in motor scores and disease staging were observed only in a subset of participants.[24] In contrast, the Belarus trial showed more consistent benefit across several symptom domains, with improvements in motor symptoms, mood, sleep, and quality of life over a three-month period.[25] Also, both studies were limited by small sample sizes and short follow-up periods. Taken together, these trials indicate that autologous BM-MSC therapy is safe and may offer symptom-improving effects in PD.[24,25] However, they highlight the need for larger, longer, and more controlled clinical studies to fully determine efficacy of autologous MSCs in treating PD.

## Allogenic MSC treatment of PD

Allogeneic BM-MSCs are a promising stem cell-based treatment for PD, offering several advantages over autologous transplantation while also presenting potential problems involving potential immune reactions.[29] Unlike autologous MSCs, which are obtained from the patient's own bone marrow, allogeneic MSCs are collected from healthy donor volunteers through bone marrow aspiration often from the posterior iliac crest.[30] These donor-derived cells can be expanded in vitro and prepared as an 'off-the-shelf' product, allowing for standardized dosing and more accessibility for use in a clinical setting.[29] However, because these cells are not from the same individual, they carry the potential risk of immune reactions or the development of donor-specific antibodies.[29] However, BM-MSCs are naturally immunomodulatory because they express very low levels of MHC class II and costimulatory molecules that are normally required to activate T-cells.[31] They also release anti-inflammatory factors that calm the immune response and reduce inflammation.[32] They do this because MSCs naturally function in the body as tissue-repair and injury-response cells, meaning they help control inflammation and protect damaged tissues rather than trigger immune activation.[33] Together, these features lower the chance of graft rejection after allogeneic BM-MSC transplantation. Aside from the potential for immune reaction, allogeneic MSCs remain appealing because they can be produced in uniform batches and be more readily accessible in a clinical setting.[29]

Allogeneic MSCs have been studied to determine whether they can offer anti-inflammatory, neuroprotective, or symptom-improving benefits in PD. Three notable clinical trials have been completed. These include a bilateral stereotactic delivery into the SVZ in India, a Phase I intravenous dose-escalation trial in the United States, and a subsequent randomized, double-blind Phase IIa intravenous infusion trial. These have evaluated and shown the safety, feasibility, and increase in biological activity of this donor stem-cell approach in patients with idiopathic PD.[34-36]

## Preclinical evidence

A key preclinical study supporting the use of allogeneic BM-MSCs for PD showed that human donor MSC can have neuroprotective and anti-inflammatory effects on dopaminergic neurons in rodents with 6-OHDA-induced PD. Treatment with human donor MSCs reduced microglial activation, lowered inflammatory markers, and helped preserve dopaminergic neurons.[37] Another important study using 6-OHDA toxin treated rats found that intravenous infusion of human BM-MSCs improved motor behavior and supported partial recovery of dopaminergic neurons.[38] Overall, these studies show that allogeneic BM-MSCs can be safely administered and can improve dopaminergic function as well as motor outcomes in rat models, helping provide the foundation for their use in human clinical trials.[37,38]

## Clinical trial 1: bilateral allogeneic BM-MSC transplantation into the SVZ

This 12-month long pilot study was conducted in India and published in 2012. It represented a subsequent clinical trial by the same research group that previously evaluated unilateral autologous BM-MSC transplantation for PD. This study examined the safety and feasibility of bilateral transplantation of allogeneic adult human BM-MSCs into the SVZ of patients with idiopathic PD as well as Parkinson's plus. Eight patients with idiopathic PD and four patients with Parkinson-plus syndromes were enrolled. All individuals had varying disease duration, ranging from 5 to 15 years. For this study, allogeneic BM-MSCs were obtained from healthy donor volunteers by aspirating bone marrow from the posterior iliac crest. Mononuclear cells were isolated and expanded in vitro to generate the enough allogeneic BM-MSCs for a therapeutic dose. Each patient received a total dose of $2 \times 10^6$ MSCs per hemisphere, delivered through multiple microdeposits using stereotactic procedure into the SVZ using MRI guided surgery.[34]

To monitor clinical symptoms post-operation of these MSCs, the researchers used standardized PD clinical rating scales. These included the UPDRSParts I–IV, administered in both ON- and OFF-medication states, as well as H&Y staging. Concerning neuroimaging, MRIs were done post-operation to monitor placement of the MSCs as well as monitor for any structural abnormalities such as tumors. In this study, researchers reported no adverse events, including tumor formation. Participants with idiopathic PD showed clinical improvements, with

average UPDRS scores improving by approximately 17.9% in the ON state and 31.2% in the OFF state at one year. Individuals with shorter disease (5-10 years) duration typically experienced the most notable improvement, whereas those with longer disease duration (11–15 years) showed less prominent improvements. In contrast, individuals with Parkinson-plus syndromes did not experience sustained improvement.[34]

Overall, the findings from this study supported the safety as well as feasibility of bilateral allogeneic BM-MSC transplantation into the SVZ for treatment of PD. Although improvements in UPDRS scores were present, the small sample size, lack of a control group, and inclusion of multiple diagnostic categories (idiopathic as well as Parkinson's plus) limit the strength of the conclusions made.[34]

## Clinical trial 2: phase I allogeneic BM-MSC safety study

This 12-month pilot dose-escalation study was conducted in Houston, TX, United States, and published in 2021. It evaluated the safety and tolerability of intravenous allogeneic BM-MSCs in patients with mild to moderate idiopathic PD. Twenty participants were enrolled and assigned to a single intravenous infusion of one of four increasing doses. These included $1 \times 10^6$, $3 \times 10^6$, $6 \times 10^6$ or $10 \times 10^6$ allogeneic BM-MSCs per kg body weight. Patients were followed up with at structured intervals up to 12 months post-infusion. The study was a follow-up to earlier autologous and allogeneic MSC trials in PD, shifting toward an intravenous donor cell approach for broader applicability, as opposed to surgical methods.[35]

For clinical monitoring, the investigators utilized standardized PD clinical rating scales, including the original UPDRSand the MDS–UPDRS, for assessing motor and non-motor symptoms. Assessments included OFF-medication and ON-medication motor scores, and total UPDRS/MDS-UPDRS scores. Neuroimaging consisted of MRI brain perfusion measurements to evaluate blood flow in the brain, particularly in the subthalamic nucleus in the basal ganglia and surrounding basal ganglia areas, to determine whether the MSC infusion caused any changes in brain activity.[35] These specific areas were studied as they are key parts of the motor circuit affected in PD.[39] In addition to neuroimaging, the study also collected blood samples to evaluate biological changes following treatment. These samples were used to measure inflammatory biomarkers, such as TNF-α and CCL22, as well as brain-derived neurotrophic factor (BDNF), to determine whether the MSCs had anti-inflammatory or neuroprotective effects. The study also examined immune reactions by testing for donor-specific HLA (human leukocyte antigen) antibodies in blood samples, which would indicate whether the patient's immune system was reacting against the donor stem cells.[35]

The study found that a single infusion of allogeneic BM-MSCs was safe and well-tolerated, with no severe allergic reactions or immune responses observed during the 52-week follow-up period. The most common side effects were temporary slow movement and brief increases in blood pressure. However, one patient with pre-existing lymphocytosis (abnormally high numbers of lymphocytes in the blood) developed chronic lymphocytic leukemia after the infusion was done, although it is unclear whether this was related to the treatment. In addition to clinical safety, blood biomarker testing showed reductions in inflammatory markers (such as TNF-α and CCL22) and an increase in brain-derived neurotrophic factor (BDNF) at 52 weeks, particularly in the highest-dose group. The high-dose group also experienced clinical improvement, with an average 14-point decrease in OFF-state UPDRS motor scores and a 21-point decrease in total UPDRS scores after one year. Perfusion brain MRI also showed increased blood flow in the subthalamic region in this high-dose group, suggesting improved activity and health of this region affected by PD, as well as a dose-related biological effect. Overall, the results indicate that a single intravenous dose of allogeneic MSCs is safe and potentially beneficial.[35]

Overall, the findings support that a single intravenous infusion of allogeneic BM-MSCs at doses up to $10 \times 10^6$ cells/kg is safe, well-tolerated, and doesn't cause immune reactions in patients with idiopathic PD. Despite the positive results from this study, which included decreases in inflammatory markers, increases in BDNF, improved activity in the subthalamic region of the brain, and an improvement in clinical symptoms, the trial was small and uncontrolled. It was designed primarily to evaluate safety rather than treatment efficacy.[35] Due to these limitations, and to determine whether the early biological and clinical signals seen in the Phase I trial could translate into meaningful therapeutic treatments, the same research group progressed to a more rigorous, placebo-controlled Phase IIa study.

## Clinical trial 3, a follow up trial on "phase I allogeneic BM-MSC safety study": Phase IIa – randomized, double-blind trial of IV allogeneic BM-MSCs

This 18-month randomized, double-blind, placebo-controlled Phase IIa study was conducted in Houston, TX, United States, and published in 2024. It evaluated repeated intravenous infusions of allogeneic BM-MSCs in patients with mild to moderate idiopathic PD. Forty-five participants were enrolled and randomized into three groups. One group received three infusions of $10 \times 10^6$ MSCs/kg. A second group received one placebo infusion followed by two allogeneic BM-MSC infusions. A third group received three placebo infusions. Patients were followed up at defined intervals up to 88 weeks post-infusion.[36]

For clinical monitoring, the investigators used standardized PD rating scales, specifically the MDS-UPDRSfor Parts I–IV with assessments in both OFF-medication and ON-medication states. They also used the H&Y stage to track disease severity. Neuroimaging included brain perfusion MRI to assess blood flow changes in the subthalamic nucleus and other basal ganglia regions as these are the neural circuits most affected in PD. The study also collected blood samples to evaluate changes in inflammatory biomarkers (such as TNF-α, CCL22) and neurotrophic factors (such as BDNF). These blood samples were also used to monitor for donor-specific HLA antibodies to indicate whether the patient's immune system was reacting against the donor stem cells.[36]

The results showed that intravenous allogeneic BM-MSC therapy remained safe and well-tolerated across all study groups with no significant increase in severe adverse events or immune reactions. The group receiving three allogeneic BM-MSC infusions had the highest improvement in OFF-state MDS-UPDRS total scores (≥12-point improvement) compared with placebo at both 62- and 88-weeks post infusion. Analyses of biomarkers also showed the most significant reductions in inflammatory markers as well as increases in neurotrophic factors in the group receiving three allogeneic BM-MSC infusions. Brain perfusion MRI results also demonstrated increased blood flow in the subthalamic region in the three-infusion group versus groups involving placebo infusions.[36]

Overall, the findings provide early evidence that repeated doses of allogeneicBM-MSCs may be safe and potentially effective in treating idiopathic PD when administered intravenously.[36] However, limitations of this trial include the single site design, limited sample

size, and relatively short duration for a neurodegenerative condition clinical trial mean that further larger sample size and longer duration trials are needed. But, the design of this study including dose-escalation, repeated doses, biomarker tests, tests for adverse immune reactions (HLA antibodies), and neuroimaging to evaluate blood flow through the brain lays an effective foundation for future trials that could establish definitive therapeutic benefit in PD.

## Clinical trials involving allogenic MSC treatment of PD

Across three major clinical trials investigating allogeneic BM-MSCs for treating PD, several important similarities and differences emerge regarding delivery method, dose size, biological evaluation, and clinical outcomes.[34-36] Foundational preclinical studies demonstrated that allogeneic BM-MSCs have strong neuroprotective and anti-inflammatory effects in rodent models of PD. In 6-OHDA-treated rat models, human donor MSC's reduced microglial activation, lowered inflammatory markers, and helped preserve dopaminergic neurons. Another study using 6-OHDA-treated rats showed that intravenous infusion of human BM-MSCs improved motor behavior and supported partial dopaminergic recovery, providing early evidence that these cells could safely improve both biological and functional measures relevant to human disease. Together, these findings helped justify the move into early human trials.[37,38]

One of the earliest clinical studies, conducted in India, used bilateral stereotactic implantation of donor MSCs into the SVZ at a fixed dose of $2 \times 10^6$ cells per hemisphere and found clinical improvement mainly in individuals with idiopathic PD. In contrast, the U.S. Phase I trial shifted to intravenous delivery and evaluated four escalating doses up to $10 \times 10^6$ MSCs/kg while also incorporating assessments of inflammatory biomarkers, neurotrophic factors, and donor-specific HLA antibodies, measures not included in the SVZ trial. The Phase IIa randomized, double-blind trial expanded on these findings by administering three high-dose infusions ($10 \times 10^6$ MSCs/kg) and using a placebo group to better evaluate efficacy. Across all three trials, no tumors or severe immune reactions were reported, consistent with the safety observed in preclinical models.[34-36]

Although study designs differed, all trials showed that allogeneic BM-MSC therapy is safe, well tolerated, and biologically active.[34-36] However, the degree of clinical improvement varied. In the SVZ study, benefits were most notable in individuals with shorter disease duration.[34] In the Phase I intravenous trial, the strongest reductions in inflammatory biomarkers, increases in BDNF, and improvements in subthalamic blood flow occurred in the highest-dose group.[35] The Phase IIa trial strengthened this dose-dependent pattern, with participants receiving three MSC infusions showing the greatest improvements in OFF-state MDS-UPDRS scores and the largest biological changes compared with placebo.[36] Overall, the preclinical and clinical evidence collectively supports the potential of allogeneic BM-MSC therapy while emphasizing the need for larger, controlled trials to determine long-term therapeutic benefit.[34-39]

## Human embryonic stem cell treatment of PD

Pluripotent stem cells are stem cells that can differentiate into any cell in the body. One type of pluripotent stem cell is hESCs. HESCs are derived from the inner cell mass of a blastocyst, an early-stage embryo that forms around 5–6 days after fertilization in humans.[3] These human embryonic stem cell lines are typically established from surplus embryos donated from in vitro fertilization (IVF) procedures with informed consent from donors.[40] With the ability of these cells to differentiate into any cell in the body, they have the potential to differentiate into various neural cells, offering some promise for dopaminergic neuronal replacement and restoration of movement-control function in individuals with PD.[3] HESCs (hESCs) have major advantages because they are pluripotent and can renew themselves indefinitely.[41,42] However, they also have disadvantages including ethical concerns due to embryo destruction, the risk of immune rejection, and the potential for tumor formation or genetic instability during long-term culture.[43,44]

A preclinical trial in primates using human parthenogenic embryonic stem cells preceded three notable clinical trials and provided early evidence supporting the safety as well feasibility of the approach of injecting dopaminergic neuron progenitors derived from embryonic stem cells into the putamen.[45] Three notable clinical trials occurred after the preclinical primate trial, all of them following a similar procedure of injected hESC-derived dopaminergic neuron progenitors into the putamen. Two of these have successfully been completed and demonstrate safety, feasibility, and efficacy of this treatment in individuals with PD.[46,47] However, one is still ongoing (Figure 4).[48]

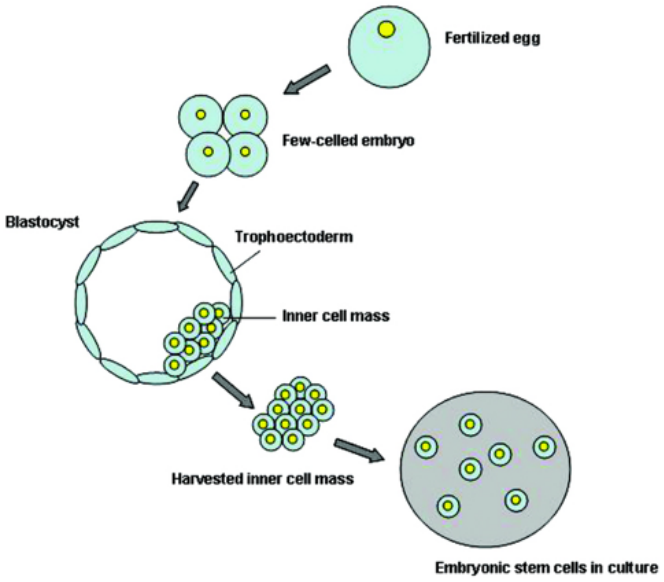


**Figure 4** The process of retrieving human embryonic stem cells for treatment of PD.[52]

## Preclinical evidence

A key preclinical study supporting the use of hESC-derived dopaminergic progenitors for PD involved the development of a clinical-grade stem-cell line from human parthenogenic embryonic stem cells that was efficiently differentiated into midbrain dopaminergic neurons.[45] Human parthenogenetic embryonic stem cells share the core biological properties of hESCsincluding pluripotency and stable genetic profiles. Because of this close similarity, the preclinical evidence generated using human parthenogenetic embryonic stem cell-derived dopaminergic progenitors is highly relevant and directly translatable to human embryonic stem cell–based clinical trials in PD.[49] In MPTP toxin-induced Parkinsonian monkey models, transplantation of these dopaminergic progenitors into the putamen resulted in survival of these dopaminergic neuron progenitors without evidence of tumor formation. The transplanted cells matured into functional DA-producing neurons and re-established dopaminergic innervation in the host brain. Motor performance in the monkeys significantly improved after transplantation as well, showing clinical symptom improvement. Overall, this study provided evidence that embryonic

**Citation:** Wickham B, Gallicchio VS. Stem cell use in treating Parkinson's disease. *J Stem Cell Res Ther.* 2026;11(1):25–36.
DOI: 10.15406/jsrt.2026.11.00216

stem cell-derived dopaminergic progenitors can be safely implanted, survive long-term, and can restore dopaminergic function in a primate model. Thus laying the essential groundwork for translation into human clinical trials.[45]

## Clinical trial 1: Bemdaneprocel (MSK-DA01) - hESC-derived midbrain dopaminergic progenitor trial in the United States and Canada.

This Phase I open-label clinical trial was conducted at multiple clinical centers for 18 months in the United States and Canada and published in 2023. It evaluated the safety and feasibility of transplanting hESC-derived dopaminergic neuron progenitor cells into the putamen of individuals with moderate PD. A total of twelve participants were enrolled across two dosing groups. The low-dose group received 0.9 million cells in both hemispheres of the putamen, and a high-dose group received 2.7 million cells in both hemispheres of the putamen. All participants underwent MRI-guided stereotactic neurosurgery for bilateral implantation of these progenitors directly into the putamen.[46]

In terms of clinical rating scales, the MDS-UPDRS particularly, researchers were interested in Part III motor symptom scores in the OFF-medication state. Neuroimaging was also used in this clinical trial, utilizing both PET and MRI. 18F-Fluoro-DOPA PET scans were to measure DA synthesis in the putamen before transplantation and at structured intervals afterward. MRI was used to monitor placement of hESC-derived dopaminergic neuron progenitors and detect structural abnormalities such as tumors. All participants were placed on one full year of immunosuppression to reduce the risk of immune rejection.[46]

The results showed the transplantation of these dopaminergic neuron progenitors were safe with no occurrence of serious adverse events or evidence of tumor formation throughout the 18-month follow-up. In the high-dose group, clinical outcomes were positive and showed OFF-state MDS-UPDRS Part III motor scores improved by approximately 23 points. This large score difference represents a large improvement in motor symptoms. 18F-Fluoro-DOPA PET scans demonstrated increased 18F-DOPA uptake in the putamen. This indicated survival, maturation, as well as integration of the transplanted dopaminergic neuron progenitors into the putamen. The low-dose cohort demonstrated smaller improvements in both motor symptoms as well as increases in DA synthesis upon 18F-Fluro-DOPA PET.[46]

Overall, this study provided strong evidence that hESC-derived dopaminergic neuron progenitor transplantation is safe, feasible, and causes increases in DA synthesis within the human putamen that suggests larger improvements with dose escalation. However, it was limited by its small sample size, open-label design, and a lack of control group.[46] But, the safety, signifying motor symptom improvement, and 18F-Fluro-DOPA Pet scan evidence of increases in DA synthesis supports progression to more controlled Phase II trials to further evaluate safety as well as efficacy of transplanted human embryonic stem cell derived dopaminergic neuron progenitors to treat PD.

## Clinical trial 2: A9-DPC (TED-A9) - hESC-derived A9-type dopaminergic progenitor trial in South Korea

This Phase 1/2a open-label clinical trial was conducted in Seoul, South Korea, and published in 2025. It evaluated the safety, feasibility, and biological activity of A9-type dopaminergic progenitor cells derived from hESCs (A9-DPC) in individuals with idiopathic PD. Twelve participants were enrolled and divided into two dose groups, a low-dose group and a high-dose group, and each underwent stereotactic bilateral implantation of the A9-DPC product into the putamen. The low-dose cohort received 3.15 million cells in both hemispheres of the putamen, whereas the high-dose cohort received 6.30 million cells in both hemispheres of the putamen.[47]

In terms of clinical rating scales, researchers used the MDS-UPDRS parts I–IV. Particularly, researchers focused on OFF-medication Part III motor scores. Neuroimaging included $^{18}$F-FP-CIT PET to evaluate DA transporter activity and 18F-FDG PET to assess metabolic changes. Scans were performed at baseline and again after transplantation to evaluate changes in DA transporter activity as well as how the transplanted dopaminergic neuron progenitors contributed to broader network activity within the brain. MRI was used to confirm accurate placement of the dopaminergic neuron progenitors and to monitor for complications such as structural abnormalities. Patients received a defined course of immunosuppressive therapy to reduce the risk of graft rejection.[47]

The results showed that transplantation of the dopaminergic neuron progenitors was safe, and no serious adverse events attributed to A9-DPC transplantation were reported throughout the follow-up period of 18 months. Clinically, participants in both dose groups showed improved motor outcomes, but the high-dose cohort demonstrated the strongest improvement. OFF-state MDS-UPDRS Part III motor scores improved by approximately 15–20 points from baseline, while the low-dose cohort improved by about 5–8 points. Total MDS-UPDRS scores showed similar improvements, most prominently in the high-dose group. Neuroimaging supported these clinical findings. 18F-FP-CIT PET scans demonstrated increased DA transporter uptake in the putamen after transplantation, with larger increasesin DAT transporter uptake in the high-dose cohort. This dose-dependent rise in DAT binding indicated that the transplanted A9-DPC cells survived and contributed to dopaminergic function. In addition, 18F-FDG PET scans revealed improved regional glucose metabolism, suggesting that the transplanted cells contributed to broader network activity rather than exerting only localized effects in the putamen where they were transplanted. Together, these imaging results provided biological evidence of integration of the dopaminergic progenitor neurons and broader network activity in the brain that paralleled the observed motor improvements.[47]

Overall, this Phase 1/2a trial provided evidence that A9-DPC transplantation may offer meaningful clinical benefit regarding improvement in motor symptoms in those with PD. As well as clinical benefit, it may offer biological benefit regarding restored presynaptic dopaminergic function and enhanced metabolic activity within motor-related brain regions. This is due to increases in MDS-UPDRS Part I–III scores as well as dose-dependent increases in DA transporter binding on 18F-FP-CIT PET and improved regional glucose metabolism showing broader network activity on 18F-FDG PET scans. However, limitations remain in this study regarding the small sample size, lack of a control group, and open-label design. Even so, the results establish a strong foundation for larger and more controlled clinical trials to determine whether hESC-derived dopaminergic neuron progenitor transplantation can provide durable, disease-improving effects in PD.[47]

## Clinical trial 3: STEM-PD - hESC-derived ventral midbrain dopaminergic progenitor trial in Europe

This clinical trial was initiated in Europe (Sweden and the UK) in 2023 and is an ongoing study designed to test a hESC-derived dopaminergic progenitor neuron product (the "STEM-PD product")

in individuals with PD. The primary aim is to assess the safety and tolerability of this stem cell therapy. The trial uses a dose-escalation scheme with two planned cohorts with the low-dose group receiving approximately 3.5 million cells in both hemispheres of the putamen and the high-dose group receiving approximately 7.1 million cells in both hemispheres of the putamen. For transplantation, participants will receive injections of the hESC-derived dopaminergic progenitors. The study is expected to enroll up to 20 participants, with each cohort advancing only after safety in the preceding group is confirmed. Long-term follow-up extends up to 36 months after transplantation to monitor safety and efficacy of the dopaminergic neuron progenitor treatment.[48]

Although the primary goal of the study is to determine safety and tolerability, the trial incorporates clinical rating scales and neuroimaging to detect biological as well as clinical benefit. Clinical rating scales include the MDS-UPDRSParts I–IV, with particular focus on OFF-medication Part III motor scores. Neuroimaging measures include DA transporter PET (such as 18F-FP-CIT to assess presynaptic dopaminergic terminal function by detecting transporters for DA and 18F-FDG PET to evaluate regional metabolic activity by detecting glucose metabolism. MRI is used to verify accurate placement of dopaminergic neuron progenitors and to monitor for any structural abnormalities.[48]

Overall, the STEM-PD trial represents one of the first efforts in Europe to clinically evaluate hESC-derived dopaminergic progenitors as a potential disease-improving therapy for PD. As an ongoing dose-escalation study with up to 20 participants, it aims to determine whether this stem-cell therapy strategy can be delivered safely and whether transplanted progenitors survive and begin to restore function of dopaminergic neurons.[48] If successful, the findings will support larger controlled trials and contribute to the development of a human embryonic stem cell regenerative therapy for Parkinson's targeting the underlying dopaminergic neuron loss in PD rather than providing only symptomatic relief like current standard treatment.

## Clinical trials involving human embryonic stem cell treatment of PD

Across the four studies involving hESCs-derived dopaminergic progenitors, several similarities and differences emerge regarding study design, cell preparation, dosing strategies, and clinical outcomes.[45-48] The preclinical human parthenogenetic embryonic stem cell-derived primate evidence provided the initial foundation for human clinical studies by demonstrating long-term survival, absence of tumor formation, and sustained improvement in motor symptoms in MPTP-induced PD.[45] These findings supported the transition into early human trials using hESC-derived dopaminergic progenitors. In one of the first human clinical trials, Bemdaneprocel, smaller doses of hESC-derived midbrain dopaminergic neuron progenitors (0.9 million vs. 2.7 million cells per putamen) were used, and clinical improvements and increases in DA synthesis on 18F-DOPA PET scans were most prominent in the high-dose group.[46] In contrast, the A9-DPC trial in South Korea used larger doses (3.15 million vs. 6.30 million cells per putamen) and showed dose-dependent increases in OFF-state MDS-UPDRS Part III scores as well as increases in DA transporter binding and regional glucose metabolism on two forms of PET scans.[47] Although both trials demonstrated safety and biological activity, the larger doses used in the A9-DPC trial were associated with stronger clinical improvements.[46,47] The ongoing STEM-PD trial in Europe builds on these findings by administering the largest planned doses of hESC-derived ventral midbrain dopaminergic progenitors (approximately 3.5 million vs. 7.1 million cells per putamen) and includes up to twenty participants.[48] Thus, allowing for a more structured evaluation of dose-escalation and long-term effect of transplanted dopaminergic neuron progenitors over a thirty-six-month period.[48]

Despite differences in dosing size, human embryonic cell lines used, and neuroimaging methods used, all studies demonstrated consistent safety with no reports of tumor formation on MRI, or immune complications on MRI. Each trial also used similar clinical rating scales, particularly OFF-state MDS-UPDRS Part III motor scores which allowed for comparison of motor symptom improvement across studies.[46-48] However, the neuroimaging types differed slightly across studies. The Bemdaneprocel clinical trial relied on 18F-DOPA PET to assess DA synthesis, whereas A9-DPC incorporated both 18F-FP-CIT PET and 18F-FDG PET to evaluate DA transporter activity and broader metabolic changes.[46,47] The STEM-PD clinical trial will also use these imaging approaches to assess graft survival and functional activity once participants reach later follow-up timepoints.[48]

Overall, although each study used different stem cell lines, doses, and evaluation methods, they collectively demonstrate that hESC-derived dopaminergic progenitors are safe, biologically active, and capable of producing notable early improvements in motor symptoms. These trials highlight the potential for these stem-cell-derived dopaminergic progenitors to serve as a disease-improving therapy for PD, while also emphasizing the need for larger, controlled studies to confirm these positive early results.[45-48]

## Induced pluripotent stem cell treatment of PD

IPSCs (iPSCs) are stem cells derived from adult somatic cells that have been genetically reprogrammed back into an embryonic stem cell–like state, giving them the ability to differentiate into any cell type.[50] This cell type is especially valuable in clinical applications for treating PD because it allows for the generation of dopaminergic neuron progenitors without the same risk of immune rejection as hESCs, fewer ethical concerns since the cells are not derived from embryos, and reliance on easily accessible cell sources such as skin or blood cells. However, iPSCs also come with important disadvantages in clinical settings. These include high variability and inconsistent quality among iPSC lines, as well as a potential risk of tumorigenesis resulting from genetic instability introduced during the reprogramming process (Figure 5).[51]

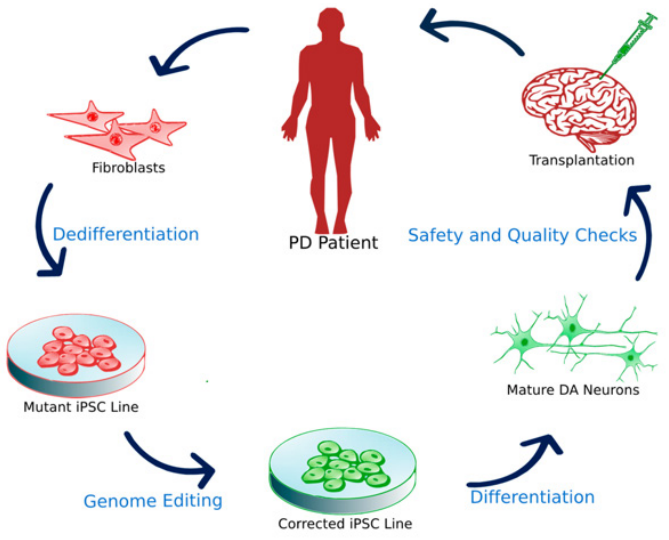


**Figure 5** The process of retrieving induced pluripotent stem cells for treatment of PD.[56]

**Citation:** Wickham B, Gallicchio VS. Stem cell use in treating Parkinson's disease. *J Stem Cell Res Ther.* 2026;11(1):25–36.
DOI: 10.15406/jsrt.2026.11.00216

## Autologous induced pluripotent stem cell treatment of PD

Autologous iPSCs represent a highly personalized stem-cell–based strategy for treating PD.[52] Autologous iPSCs are generated directly from the patient's own somatic cells. Because the resulting dopaminergic progenitors are genetically matched to the patient, this approach minimizes the risk of immune rejection and may reduce or eliminate the need for long-term immunosuppression.[53]

An in-human clinical application of autologous iPSC-derived dopaminergic progenitors was carried out in the United States and followed the patient for 24 months. In this study, skin fibroblasts from an individual with idiopathic PD were reprogrammed into iPSCs and differentiated into midbrain dopaminergic progenitors. Transplantation occurred through two stereotactic surgeries spaced six months apart, with the first graft placed in the left putamen and the second in the right putamen. Clinical assessments included the MDS-UPDRSParts I–IV, with particular focus on Part III motor scores. Neuroimaging with 18F-DOPA PET evaluated DA synthesis and biological activity of the grafted cells. Over the 24-month period, motor function showed modest improvement, and PET imaging demonstrated increasing 18F-DOPA uptake near the graft sites, suggesting survival, maturation, and dopaminergic function of the autologous iPSC-derived progenitors.[52]

## Clinical trial 1: personalized iPSC-derived DA progenitor cells for PD

This human-application of autologous induced pluripotent stem cell derived midbrain dopaminergic progenitor cells was conducted in the United States for 24 months and published in 2020. The study evaluated whether autologous iPSC-derived dopaminergic progenitors could be safely generated and transplanted into an individual with idiopathic PD. Skin fibroblasts from the patient were reprogrammed into iPSCs and differentiated into midbrain dopaminergic progenitors. For transplantation, it was done over the course of two surgeries and six months. The first surgery implanted the iPSC-derived dopaminergic progenitors into the left putamen, followed six months later by implantation into the right putamen.[52]

Clinical follow-up continued for nearly two years after the second surgery and included clinical rating scales and neuroimaging. The clinical rating scales included MDS-UPDRS Parts I-IV, with researchers especially focusing on Part III scores. Neuroimaging included 18F-DOPA PET to evaluate DA synthesis.[52]

Clinically, rating scale results revealed some improvement in motor symptoms based on changes in MDS-UPDRS Part III scores in both OFF- and ON-medication states. Neuroimaging results supported biological activity of the autologous iPSC-derived dopaminergic neuron progenitors. 18F-DOPA PET scans showed a modest decline in DA synthesis shortly after the first implantation but demonstrated a gradual and sustained increase beginning several months after the second implantation. By 24 months after the initial surgery, increases in 18F-DOPA uptake were most prominent in the putamen near the areas where the dopaminergic neuron progenitors were transplanted, suggesting that the transplanted progenitor cells matured into dopaminergic neurons capable of synthesizing DA.[52]

Overall, this study demonstrated that autologous iPSC-derived dopaminergic progenitor transplantation is feasible, safe, and capable of surviving long-term in the human brain. The increases in DA synthesis on PET imaging as well as the mild clinical improvement suggest biological activity of transplanted dopaminergic neuron progenitors. However, because this was a single-patient study, its findings cannot be generalized or interpreted as evidence of treatment efficacy. However, the results provided an important foundation for the development of future clinical trials investigating autologous iPSC-based dopaminergic cell replacement therapies for PD.[52]

## Allogeneic induced pluripotent stem cell treatment of PD

Allogeneic iPSCs represent a promising stem-cell–based strategy for treating PD.[54,55] Unlike autologous iPSCs, which are generated from the patient, allogeneic iPSC-derived dopaminergic progenitors are created from healthy donor cell lines and expanded, allowing for more widespread clinical availability.[56] A key preclinical study supporting this approach demonstrated that human iPSCs can be differentiated into dopaminergic progenitors and safely transplanted into mouse models of PD. Once these dopaminergic neuron progenitors were transplanted, they survived and matured into DA-producing neurons. Corresponding with this increase in dopaminergic activity, improvements in motor behavior occurred. These findings provided evidence that allogeneic iPSC-derived dopaminergic progenitors can restore dopaminergic function in vivo. Overall, this trial helped establish the foundation for early human clinical trials.[55]

Building on this preclinical work, the first formal Phase I/II clinical trial investigating allogeneic iPSC-derived dopaminergic progenitors for PD was conducted at Kyoto University Hospital in Japan and followed patients for 24 months. In this study, seven individuals with idiopathic PD underwent bilateral stereotactic transplantation of donor-derived iPSC-derived midbrain dopaminergic progenitors into the putamen. Participants received either a low dose of 2.1–2.6 million dopaminergic progenitors per hemisphere or a high dose of 5.3–5.5 million cells per hemisphere. Clinical assessments included MDS-UPDRS Parts I–IV to evaluate changes in non-motor symptoms, activities of daily living, motor function, and treatment complications, while neuroimaging with MRI and 18F-DOPA PET monitored graft placement, structural abnormalities, and DA synthesis over the 24-month follow-up period.[54]

## Preclinical evidence

A key preclinical study supporting allogeneic induced pluripotent stem cell therapy for PD involved the development of a human induced pluripotent stem cell line that was differentiated into dopaminergic progenitors. When these dopaminergic progenitors were transplanted into mice, there were no signs of tumor formation. In 6-OHDA treated rat models of PD, the dopaminergic progenitor cells survived, matured into DA-producing neurons, and improved motor behavior. Overall, this study provided important evidence that allogeneic human iPSC-derived dopaminergic progenitors can be safely transplanted and can restore dopaminergic function in animal models. Thus, laying the groundwork for translation into human clinical trials.[55]

## Clinical trial 1: Phase I/II trial of iPS-cell-derived dopaminergic cells for PD

An early formal Phase I/II clinical trial of iPSC-derived dopaminergic progenitors in PD was conducted for 24 months at Kyoto University Hospital, Japan. Seven patients (50–69 years old) with idiopathic PD of at least 5 years duration, L-DOPA responsive, and with motor complications underwent bilateral transplantation of allogeneic iPSC-derived midbrain dopaminergic progenitor cells into the putamen. These dopaminergic progenitors were delivered stereotactically into the putamen. Three of the participants received the low dose of 2.1-2.6 million dopaminergic progenitors in both

hemispheres of the putamen. Four of the participants received the high dose of 5.3-5.5 million dopaminergic progenitors in both hemispheres of the putamen.[54]

Clinical rating scales used in this study included MDS-UPDRS Parts I-IV to evaluate changes in non-motor symptoms, ability to do activities of daily living, changes in motor symptoms, and complications of standard PD therapy. Neuroimaging included MRI as well as 18F-DOPA PET. MRI was used to confirm placement of the dopaminergic neuron progenitors and to monitor for structural changes such as tumors over the 24 months of the study. 18-F-DOPA PET was used to monitor presynaptic DA synthesis to evaluate biological activity of DAsynthesis of the transplanted dopaminergic neuron progenitors.[54]

Clinically, MDS-UPDRS Part III motor scores improved by around 20% in the OFF-medication state and around 36% in the ON state after 24 months. No dopaminergic neuron progenitor-related serious adverse events or tumor formation were detected on MRI or clinical exam during the 24-month follow up, showing the safety of transplanting these dopaminergic neuron progenitors. Neuroimaging showed clear dopaminergic activity of the allogeneic iPSCs. At 24 months, 18F-DOPA PET uptake in the putamen increased by around 44.7% on average, with a larger around 63.5% increase in the high-dose group.[54]

Overall, this study demonstrated that transplantation of allogeneic iPSC-derived dopaminergic progenitors into the putamen is feasible, safe, and shows clinical as well as dopaminergic improvement in individuals with PD through improvements in MDS-UPDRS Part III scores and increased DA synthesis upon 18F-DOPA PET scans.[54]

However, because this was an open-label, early-phase study with a small number of participants and no control group, its findings cannot be generalized or interpreted as definitive proof of long-term therapeutic efficacy of allogeneic iPSCs for PD. Nonetheless, the results provide a foundation for larger, controlled clinical trials to further evaluate the safety and efficacy of allogeneic iPSC-based dopaminergic neuron treatment in PD.[54]

## Summary and conclusion

PD is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to reduce DA transmission to the basal ganglia and the development of hallmark motor symptoms. This dopaminergic neuron loss results from multiple interacting mechanisms that contribute to impaired DA synthesis and signaling. Over time, the putamen is especially affected because it relies heavily on DA to help control movement. Preclinical studies using stem cell-derived dopaminergic neuron progenitors have consistently shown that transplanted cells can survive, mature, and restore DA release in animal models, leading to improvements in motor behavior. These findings, alongside early clinical evidence showing dopaminergic neuron progenitor survival as well improvements in dopaminergic activity and clinical symptoms in human participants highlight the potential of regenerative medicine as a treatment for PD.

Looking ahead, advancing PD treatment will require improving stem-cell based treatments and redesigning clinical trials to better test these therapies. Future trials should work to identify the most effective dose and delivery method for stem-cells. To fully understand how well these therapies work, studies need larger participant groups and longer follow-up periods. Overall, these changes will help move stem-cell treatments of PD from early research into reliable treatment options for people with PD.

## Acknowledgements

None

## Conflicts of interest

The authors declare that there are no conflicts of interest.

## References

1. Mayo Clinic Staff. Parkinson's disease: symptoms and causes. Mayo Clinic. 2026.
2. Triarhou LC. Dopamine and Parkinson's disease. In: *Madame Curie Bioscience Database*. Landes Bioscience. 2013.
3. Daubner SC, Le T, Wang S. Tyrosine hydroxylase and regulation of dopamine synthesis. *Arch Biochem Biophys*. 2011;508(1):1–12.
4. Penn Medicine. Dementia with Lewy bodies. Penn Medicine. 2026.
5. Johns Hopkins Medicine. Lewy body dementia (LBD). Johns Hopkins Medicine. 2022.
6. Qu Y, Huang Y, Zhang Z, et al. A systematic review and meta–analysis of inflammatory biomarkers in Parkinson's disease. *NPJ Parkinsons Dis*. 2023;9(1):18.
7. Palasz E, Wysocka A, Gasiorowska A, et al. BDNF as a promising therapeutic agent in Parkinson's disease. *Int J Mol Sci*. 2020;21(3):1170.
8. Bathina S, Das UN. Brain–derived neurotrophic factor and its clinical implications. *Arch Med Sci*. 2015;6(6):1164–1178.
9. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. *Neuron*. 2003;39(6):889–909.
10. Tanner CM, Ostrem JL. Parkinson's disease. *N Engl J Med*. 2024;391(5):442–452.
11. Freitas ME, Lopez MR, Fox SH. Motor complications of dopaminergic medications in Parkinson's disease. *Semin Neurol*. 2017;37(2):147–157.
12. Friedman JH. Atypical Parkinsonism & Parkinson plus syndromes. American Parkinson disease association. 2024.
13. Mayo Clinic Staff. Stem cells: what they are and what they do. Mayo Clinic. 2026.
14. Physiopedia. Hoehn and Yahr scale. 2026.
15. Goetz CG, Tilley BC, Shaftman SR, et al. Movement disorder society–sponsored revision of the unified Parkinson's disease rating scale (MDS–UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. 2008;23(15):2129–2170.
16. American physical therapy association. Unified Parkinson's disease rating scale (UPDRS) and MDS–UPDRS. American physical therapy association. 2018.
17. Movement disorder society task force on rating scales for Parkinson's disease. The unified Parkinson's disease rating scale (UPDRS): status and recommendations. Movement disorder society. 2003.
18. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant*. 2011;20(1):5–14.
19. Li C, Zhao H, Cheng L, et al. Allogeneic vs autologous mesenchymal stem/stromal cells in their medication practice. *Cell Biosci*. 2021;11(1):187.
20. Joyce N, Annett G, Wirthlin L, et al. Mesenchymal stem cells for the treatment of neurodegenerative disease. *Regen Med*. 2010;5(6):933–946.
21. Ullah I, Subbarao RB, Rho GJ. Human mesenchymal stem cells-current trends and future prospective. *Biosci Rep*. 2015;35(2):e00191.
22. Crigler L, Robey RC, Asawachaicharn A, et al. Human mesenchymal stem cell subpopulations express a variety of neuro–regulatory molecules and promote neuronal cell survival and neuritogenesis. *Exp Neurol*. 2006;198(1):54–64.

23. Weiss ML, Troyer DL. Stem cells in the umbilical cord. *Stem Cell Rev*. 2006;2(2):155–162.

24. Venkataramana NK, Kumar SKV, Balaraju S, et al. Open–labeled study of unilateral autologous bone marrow–derived mesenchymal stem cell transplantation in Parkinson's disease. *Transl Res*. 2010;155(2):62–70.

25. Boika A, Sokolik V, Kazlou D, et al. Mesenchymal stem cells in Parkinson's disease: motor and nonmotor symptoms in the early posttransplant period. *Surg Neurol Int*. 2020;11:380.

26. Chen DD, Fu W, Zhang PP, et al. Therapeutic effects of intranigral transplantation of mesenchymal stem cells in rat models of Parkinson's disease. *J Neurosci Res*. 2017;95(3):907–917.

27. Hayashi T, Wakao S, Kitada M, et al. Autologous mesenchymal stem cell–derived dopaminergic neurons function in Parkinsonian macaques. *J Clin Invest*. 2013;123(1):272–284.

28. Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron*. 2011;70(4):687–702.

29. Velikova T, Dekova T, Miteva DG, et al. Controversies regarding transplantation of mesenchymal stem cells. *World J Transplant*. 2024;14(2):90554.

30. Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow–derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. *JAMA*. 2012;308(22):2369–2379.

31. Shi M, Liu ZW, Wang FS. Immunomodulatory properties and therapeutic application of mesenchymal stem cells. *Clin Exp Immunol*. 2011;164(1):1–8.

32. Huang Y, Li Q, Zhang K, et al. Immunomodulatory mechanisms of mesenchymal stem cells and their potential clinical applications. *Int J Mol Sci*. 2022;23(17):10023.

33. Vohra M, Arora SK. Mesenchymal stem cells-the master immunomodulators. *Explor Immunol*. 2023;3:104–122.

34. Venkataramana NK, Pal R, Rao SA, et al. Bilateral transplantation of allogenic adult human bone marrow–derived mesenchymal stem cells into the subventricular zone of Parkinson's disease: a pilot clinical study. *Stem Cells Int*. 2012;2012:931902.

35. Schiess MC, Eldabe S, Furr–Stimming E, et al. Allogeneic bone marrow–derived mesenchymal stem cell safety in idiopathic Parkinson's disease. *Mov Disord*. 2021;36(8):1825–1834.

36. Schiess MC, Suescun J, Lemus JDM, et al. Allogeneic bone marrow–derived mesenchymal stem cells for Parkinson's disease: a randomized trial. *Mov Disord*. 2025;40(12):2688–2699.

37. Mendes–Pinheiro B, Teixeira FG, Anjo SI, et al. Bone marrow mesenchymal stem cells' secretome exerts neuroprotective effects in a Parkinson's disease rat model. *Front Bioeng Biotechnol*. 2019;7:294.

38. Oh SH, Kim HN, Park HJ, et al. Mesenchymal stem cells inhibit transmission of α–synuclein by modulating clathrin–mediated endocytosis in a Parkinsonian model. *Cell Rep*. 2016;14(4):835–849.

39. DeLong MR, Wichmann T. Basal ganglia circuits as targets for neuromodulation in Parkinson disease. *JAMA Neuro*l. 2015;72(11):1354–1360.

40. Salari S, Adashi EY, Keller L, et al. Human embryos donated for human embryonic stem cell derivation. *Fertil Steril*. 2023;119(1):3–10.

41. National Institutes of Health. Introduction to stem cells. National Institutes of Health. 2021.

42. Thomson JA, Eldor JI, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts. *Science*. 1998;282(5391):1145–1147.

43. Bellieni CV, Acampa M, Maffei M, et al. Electromagnetic fields produced by incubators influence heart rate variability in newborns. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(4):F298–F301.

44. Shankar G, Devanarayan V, Amaravadi L, et al. A risk–based bioanalytical strategy for the assessment of antibody immune responses against biological drugs. *Nat Biotechnol*. 2007;25(5):555–561.

45. Wang YK, Zhu WW, Wu MH, et al. Human clinical–grade parthenogenetic ESC–derived dopaminergic neurons recover locomotive defects of nonhuman primate models of Parkinson's disease. *Stem Cell Report*s. 2018;11(1):171–182.

46. Schweitzer JS, Song B, Herrington TM, et al. Personalized induced pluripotent stem cells for Parkinson's disease: a phase I clinical trial. *Nat Med*. 2020;26(7):1137–1145.

47. Takahashi J. Stem cell therapy for Parkinson's disease. *Curr Opin Neurobiol*. 2020;61:1–6.

48. Barker RA, Ouellet JD, Parmar M. Cell–based therapies for Parkinson disease-past insights and future potential. *Nat Rev Neurol*. 2015;11(9):492–503.

49. Kikuchi T, Morizane A, Doi D, et al. Human iPS cell–derived dopaminergic neurons function in a primate Parkinson's disease model. *Nature*. 2017;548(7669):592–596.

50. Morizane A, Kikuchi T, Hayashi T, et al. MHC matching improves engraftment of iPSC–derived neurons in nonhuman primates. *Nat Commun*. 2017;8:385.

51. Parmar M, Grealish S, Henchcliffe C. The future of stem cell therapies for Parkinson disease. *Nat Rev Neurosci*. 2020;21(2):103–115.

52. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 2007;131(5):861–872.

53. Doi D, Samata B, Katsukawa M, et al. Isolation of human induced pluripotent stem cell–derived dopaminergic progenitors by cell sorting for successful transplantation. *Stem Cell Reports*. 2014;2(3):337–350.

54. Kordower JH, Olanow CW, Dodiya HB, et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain*. 2013;136(8):2419–2431.

55. Barker RA, Barrett J, Mason SL, et al. Fetal dopaminergic transplantation trials and the future of neural grafting in Parkinson's disease. *Lancet Neurol*. 2013;12(1):84–91.

56. Kirkeby A, Nolbrant S, Tiklova K, et al. Predictive markers guide differentiation to improve graft outcome in clinical translation of hESC–based therapy for Parkinson's disease. *Cell Stem Cell*. 2017;20(1):135–148.