Dopaminergic Cell Transplantation in Parkinson's Disease: Bridging the Gap Between Animal Models and Clinical Outcomes

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Received May 18, 2026
Accepted October 27, 2026
Electronic access December 15, 2026

Affecting over eight million people, Parkinson's disease is a neurodegenerative disease characterized by neural death of dopamine-producing neurons. While the pharmaceutical treatment of Levodopa alleviates the symptoms of the disease, no therapy that addresses the root cause of the disease currently exists[1]. In this circumstance, dopaminergic cell transplantation has been proposed as a restorative cell replacement strategy aimed at replacing the lost dopaminergic neuron population. However, although dopaminergic cell transplantation consistently improves motor behavior in animal models, clinical outcomes in patients remain variable and unpredictable. This paper will examine the translational gap by analyzing recurrent failure modes observed in clinical applications, including incomplete dopaminergic identity, graft-induced dyskinesia, immune mismatch, and limited circuit integration. Rather than summarizing individual studies, mechanistic patterns that distinguish preclinical success from clinical failure will be identified. Although several challenges remain, continued advances in understanding these limitations may help improve the clinical translation of stem cell-based therapies for Parkinson's disease.

Keywords: Parkinson's disease, Dopaminergic cell transplantation, Stem cell therapy, Induced pluripotent stem cells (iPSCs), Graft-induced dyskinesia, Translational gap, Cell replacement therapy, Neurodegeneration

Introduction

Parkinson's disease is a progressive neurodegenerative disorder that is clinically diagnosed as parkinsonism, a condition of bradykinesia accompanied by rest tremor, rigidity, or both, but its pathology is not confined to the motor system[1]. The disease is defined pathologically by intraneural aggregations of misfolded alpha-synuclein, known as Lewy bodies, and postmortem staging studies show this pathology spreading in a largely predictable sequence, ascending from the lower brainstem to the substantia nigra and, only later, to the cerebral cortex[2]. This progression of the disease tracks with symptom timing in which non-motor features – including hyposmia, autonomic dysfunction, and REM sleep behavior disorder – often precede motor symptoms by years, while cognitive and neuropsychiatric symptoms tend to appear later when the pathology progresses to the cerebral cortex. Because much of this non-motor symptoms reflect neurodegeneration outside the nigrostriatal dopaminergic system, and because no pharmacologic therapy has yet shown to prevent or delay this broader course of disease[3], current treatment, both pharmacologic and cell-based, remains directed specifically at the dopaminergic component of the disease[1].

Within this dopaminergic component, the loss of neurons in the nigrostriatal pathway leads to impaired dopamine signaling and the disease's characteristic motor dysfunction[4,5] (Figure 1)

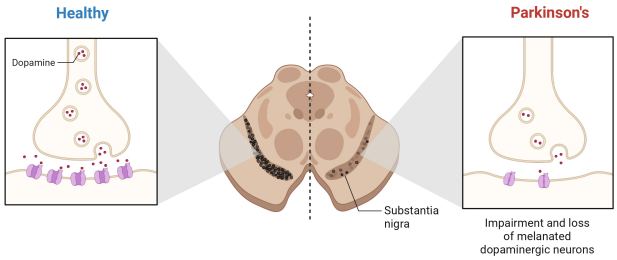


Figure. 1 Comparison of dopaminergic signaling in healthy and Parkinsonian conditions. In healthy neurons, dopamine release from the substantia nigra supports normal motor signaling, whereas Parkinson's disease is characterized by degeneration of dopaminergic neurons and reduced dopamine transmission. Created in https://BioRender.com

As illustrated in Figure 1, healthy dopaminergic neurons in the substantia nigra release dopamine to maintain normal motor signaling, while Parkinson's disease is associated with degeneration of these neurons and reduced dopamine transmission. Since this neuronal loss underlies the disease's characteristic motor symptoms, cell transplantation has been proposed

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as a restorative cell replacement strategy aimed at restoring the affected neuronal population[6]. In contrast to conventional treatments such as levodopa, dopamine agonists, MAO-B inhibitors, or deep brain stimulation that primarily alleviate the symptoms of the disease by modulating dopamine signaling[1], cell transplantation aims to replace the lost dopaminergic neurons themselves.

Throughout numerous preclinical studies, repeated successes in animal models have been reported. In rodent and non-human primate models of Parkinson's disease, transplantation of stem-cell-derived dopaminergic neurons has improved motor function, increased survival of grafted neurons, and enhanced dopamine production. These findings suggest that cell transplantation can serve as a robust and long-lasting treatment in preclinical settings[7,8]. However, despite these strong preclinical outcomes, clinical trials in Parkinson's disease patients have produced highly variable results. Recent clinical trials[9–11] using approaches such as autologous iPSC-derived dopaminergic neurons and embryonic stem cell–derived grafts have primarily focused on safety and feasibility in small patient cohorts, rather than demonstrating consistent and robust functional recovery that have been observed in preclinical studies. Moreover, numerous issues have been reported, including incomplete dopaminergic identity of grafted cells, modest motor improvement, and graft-induced dyskinesia[12–14]. Particularly, graft-induced dyskinesia has been reported in a subset of patients following fetal dopaminergic transplantation, although the reported incidence varies across studies. This wide range reflects the inconsistency of clinical outcomes[15]. Therefore, understanding and addressing this translational gap is vital for the development of effective and safe stem cell–based therapies for Parkinson's disease[16] (Figure 2).

The goal of this paper is to examine why dopaminergic cell transplantation shows consistent success in preclinical models but remains difficult to translate in clinical settings. This review focuses on some key challenges seen in patients, including incomplete dopaminergic identity, variability in functional outcomes, and the occurrence of graft-induced dyskinesia. By outlining these limitations, this paper aims to provide a clearer understanding of the factors that influence clinical translation and to highlight considerations for improving future therapeutic strategies.

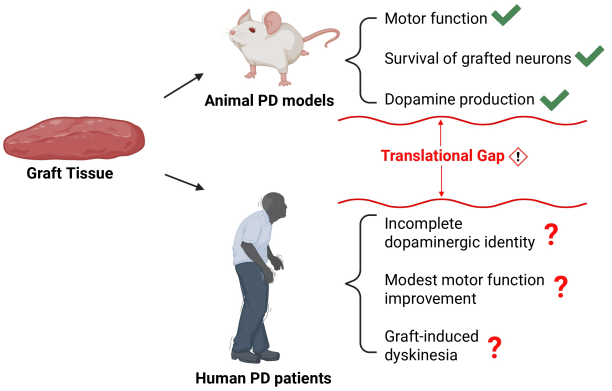


Figure. 2 Overview of the translational gap between preclinical and clinical outcomes in dopaminergic cell transplantation for Parkinson's disease. In animal models, stem cell–derived dopaminergic neuron transplantation has consistently demonstrated improved motor function, graft survival, and dopamine production. In contrast, clinical studies in Parkinson's disease patients have reported variable functional outcomes, incomplete dopaminergic identity, and graft-induced dyskinesia. Created in https://BioRender.com

Method - Literature Search

Literature Search Strategy

A literature search was conducted in PubMed to identify studies examining dopaminergic cell transplantation and cell replacement approaches for Parkinson's disease. The final search was performed on August 29, 2026, and was restricted to publications from 1990 through 2026. The primary search strategy was designed to identify studies involving dopaminergic cell transplantation and stem cell-based approaches. Because graft-induced dyskinesia (GID) represents an important complication of dopaminergic cell transplantation, a supplementary search specifically targeting GID was also performed. Information regarding ongoing and completed clinical trials was additionally verified using ClinicalTrials.gov.

The complete Boolean search string used for the primary PubMed search was:

("Parkinson Disease"[Mesh] OR "Parkinson's disease"[Title/Abstract] OR "Parkinson disease"[Title/Abstract]) AND ("dopaminergic neuron transplantation"[Title/Abstract] OR "dopaminergic cell transplantation"[Title/Abstract] OR "dopamine neuron transplantation"[Title/Abstract] OR "dopaminergic cell replacement"[Title/Abstract] OR "cell replacement therapy"[Title/Abstract] OR "neural transplantation"[Title/Abstract] OR "dopaminergic progenitor"[Title/Abstract] OR "dopaminergic progenitors"[Title/Abstract]) AND ("stem cell"[Title/Abstract] OR "stem cells"[Title/Abstract] OR "induced pluripotent stem cell"[Title/Abstract] OR "induced pluripotent stem cells"[Title/Abstract] OR iPSC[Title/Abstract] OR iPSCs[Title/Abstract] OR "embryonic stem cell"[Title/Abstract] OR "embryonic stem cells"[Title/Abstract] OR fetal[Title/Abstract] OR foetal[Title/Abstract] OR graft*[Title/Abstract] OR transplant*[Title/Abstract]).

The supplementary GID-focused search used:

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("Parkinson Disease"[Mesh] OR "Parkinson's disease"[Title/Abstract] OR "Parkinson disease"[Title/Abstract]) AND ("graft-induced dyskinesia"[Title/Abstract] OR "graft induced dyskinesia"[Title/Abstract] OR "graft-induced dyskinesias"[Title/Abstract]) AND (transplant*[Title/Abstract] OR graft*[Title/Abstract] OR "cell transplantation"[Title/Abstract] OR "neural transplantation"[Title/Abstract]).

Eligibility Criteria and Study Selection

Studies were considered for inclusion if they provided relevant evidence or context regarding dopaminergic cell transplantation for Parkinson's disease, including preclinical studies, clinical studies, and review articles addressing cell sources, transplantation outcomes, therapeutic efficacy, safety, graft-induced dyskinesia, or challenges associated with cell replacement therapy. Studies were excluded if they (1) were unrelated to Parkinson's disease; (2) did not address dopaminergic cell transplantation or relevant aspects of cell replacement therapy; (3) focused exclusively on other therapeutic approaches, such as pharmacological, gene-based, or surgical interventions, without a relevant cell transplantation component; or (4) did not provide information relevant to the scope of this review.

Records from the two PubMed searches were combined and deduplicated using PubMed identifiers (PMIDs). Unique records were screened by title and abstract, followed by full-text assessment of potentially eligible articles. The study selection process was documented according to PRISMA 2020 and is presented in the PRISMA flow diagram (Figure 1).

Data Extraction

Data were extracted from each included study and organized in a study-level evidence table. Extracted information included study design, experimental model or patient population, cell source and type, transplantation site, follow-up period, and key efficacy and safety outcomes.

Quality Assessment

The quality of included studies was assessed based on study design, sample size, presence of appropriate controls, duration of follow-up, and completeness of outcome and safety reporting. These factors were considered when interpreting the strength and limitations of the available evidence.

Study Selection

The two PubMed searches identified 682 records. After removal of 20 duplicate records, 662 unique records remained for screening. Publications were assessed for relevance to the scope of this review, and 37 publications were ultimately incorporated into the narrative review. In addition, three ClinicalTrials.gov records were consulted to verify information regarding ongoing clinical trials, resulting in 40 total sources cited in the manuscript. The literature selection process is summarized in Figure 3.

Results

Preclinical success in animal model

Preclinical studies have demonstrated that transplanted dopaminergic neurons can survive, mature, and restore function in animal models of Parkinson's disease.

In one preclinical study[17], human pluripotent stem cell–derived midbrain dopaminergic progenitors were transplanted into 6-OHDA–lesioned rat models. The grafted cells survived, differentiated into dopaminergic neurons, and integrated into host brain tissue. Motor function improved beginning at 12–16 weeks post-transplantation, with near-complete recovery by 20–24 weeks, supported by behavioral assays. Histological analysis showed robust graft survival with thousands of TH^+ neurons, along with projection, synaptic integration, and dopamine production.

In another study[18], clinical-grade human iPSC-derived dopaminergic progenitors were transplanted into 6-OHDA–lesioned rats. Following transplantation of 4×10^5 cells per rat, animals showed progressive motor recovery, with rotational asymmetry returning to near-normal levels by 16 weeks, while controls showed no improvement. Histological analysis confirmed graft survival with $2{,}835 \pm 2{,}534$ TH^+FOXA2^+ neurons and axonal outgrowth into the host striatum. Similar graft survival was observed in an MPTP-treated monkey model at 6 months post-transplantation.

In a third study[19], human embryonic stem cells–derived ventral midbrain progenitors were transplanted into 6-OHDA–lesioned rats after 10 days of differentiation. The grafts were neuron-rich, tumor-free, and maintained regional identity. These cells generated a higher proportion of dopaminergic progenitors (81% vs. 21%) and produced more TH^+ neurons ($8{,}338 \pm 1{,}920$ vs. 558 ± 119 per 100,000 cells). Functionally, the grafts released dopamine and reversed motor deficits by 12–16 weeks, while control grafts showed no improvement.

Together, these studies demonstrate robust graft survival and functional recovery in preclinical models, although important translational limitations remain, particularly regarding long-term safety, primate validation, and clinical reproducibility (Table 1). A further caveat applies across all three of these preclinical studies, where each relied on the 6-ODHA rat model, in which a toxin produces an acute, non-progressive dopaminergic lesion. This model does not reproduce the

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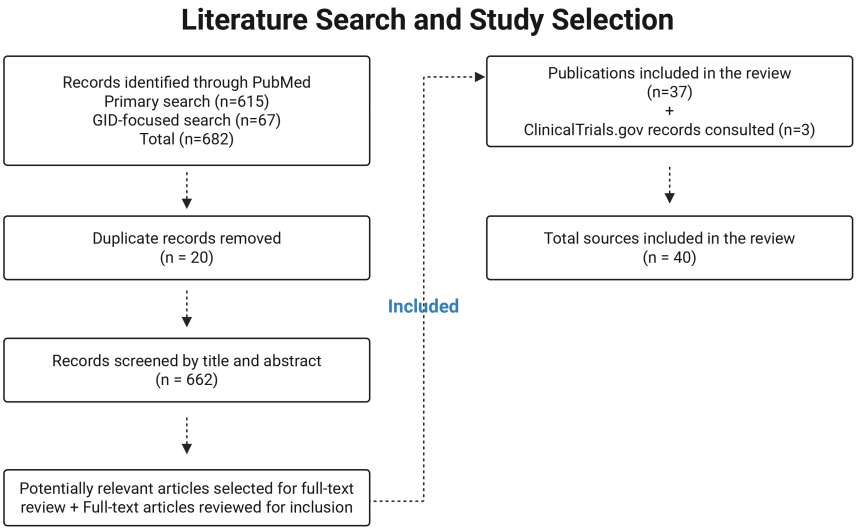


Figure. 3 Flow diagram of the literature search, screening, and study selection process for this review

slow, progressive, alpha-synuclein-driven neurodegeneration that characterizes human Parkinson's disease. Consequently, the motor recovery observed after grafting in these studies reflects rescue of a static, toxin-induced lesion rather than reversal of an ongoing degenerative process, which limits how directly these findings translate to human disease.

Variability in clinical outcomes

Despite these promising preclinical outcomes, clinical trials in patients with Parkinson's disease have produced highly variable results. However, it is important to note that only two of the five studies summarized in Table 2 evaluated the defined, stem-cell-derived products characterized preclinically in Table 1. The remaining three used fetal ventral mesencephalic tissue grafts, which are materially different products with no corresponding preclinical study in Table 1. Each product class is therefore considered separately below and compared against the preclinical study that shares the product-class.

For example, a recent Phase I/II clinical trial conducted at Kyoto University[20] evaluated iPSC-derived dopaminergic progenitor transplantation in seven patients without a control group. This trial used the same clinical-grade, HLA-homozygous iPSC line characterized preclinically by Doi *et al.* (2020, Table 1)[18]. That preclinical study reported a dopaminergic progenitor population free of residual undifferentiated cells and free of tumorigenicity or toxicity in immunodeficient mice, along with reversal of rotational asymmetry in 6-OHDA-lesioned rats by 16 weeks post-transplantation. Efficacy, assessed in the six patients who completed evaluation, varied substantially, displaying that three patients showed marked improvement in the MDS-UPDRS Part III "off" score at 24 months (32.4%, 45.1%, and 50.0%), a fourth improved by 9.1%, and two patients showed no improvement at all, for an average change of 20.4% across the cohort[20]. Particularly, the two patients who did not improve included the oldest participant in the trial, while the youngest patient showed the greatest benefit, consistent with the pattern seen in earlier fetal-tissue trials. However, such small sample sizes make it difficult to determine whether observed changes are truly treatment-related or simply reflect individual variability among patients. In addition, without a control group, any observed improvement could not be clearly separated from placebo effects, spontaneous fluctuations in symptoms, or the natural progression of the disease over time. This limitation is particularly important in Parkinson's disease, where clinical outcomes often rely on behavioral and motor assessments that can fluctuate and be influenced by patient expectation. Furthermore, because the study was non-randomized, differences in baseline disease severity across patients could also influence the results. The open-label design introduces an additional limitation, since both patients and investigators were aware of the treatment, which can bias symptom reporting and clinical evaluation.

The autologous iPSC-derived stream can similarly be compared with its matching preclinical study. Schweitzer *et al.* (2020)[21] reported the first-in-human application of a personalized, patient-derived iPSC platform in a single patient, who showed gradual improvement in motor and quality-of-life scores over 18-24 months without dyskinesia. However, the absence of controls and the sample size (n=1) prevent con-

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Table 1: Summary of Preclinical Studies Evaluating Stem Cell–Derived Dopaminergic Neuron Transplantation in Parkinson's Disease Models

Study	Transplanted Cell Type	Evidence of Graft Survival/ Integration	Evidence of Functional Recovery	Key Limitation
Song *et al*., 2020 [17]	hPSC-derived midbrain dopaminergic progenitors	TH^+ neuron survival, synaptic integration, dopamine production	Near-complete behavioral recovery by 20-24 weeks	Tumorigenic risk from residual undifferentiated iPSCs, requiring an additional purification step to mitigate
Doi *et al*., 2020 [18]	Clinical-grade hiPSC-derived dopaminergic progenitors	TH^+FOXA2^+ neuron survival and axonal outgrowth	Rotational asymmetry normalized by 16 weeks	Substantial inter-animal variability in dopaminergic neuron yield/survival despite a standardized transplantation protocol
Kirkeby *et al*., 2012 [19]	hESC-derived ventral midbrain progenitors	High dopaminergic progenitor yield and tumor-free grafts	Reversal of motor deficits by 12-16 weeks	Very short (as short as 10 days) in vitro differentiation before transplantation, incomplete midbrain progenitor purity (˜81% FOXA2+/LMX1A+in vitro), and follow-up limited to 18 weeks post-transplantation

clusions about reproducibility. This same platform was characterized preclinically by Song *et al*. (2020, Table 1) [17], including tumorigenicity testing and behavioral recovery in an animal model.

On the other hand, no published clinical outcomes are yet available for the allogeneic hESC-derived stream represented preclinically by Kirkeby *et al*. (2012, Table 1) [19]. A corresponding first-in-human trial using this hESC-derived product (STEM-PD) is registered and ongoing [10], and its results will be required to complete this product-by-product comparison.

By contrast, the following three trials evaluated fetal ventral mesencephalic tissue grafts rather than a defined stem-cell product, and none has a matching preclinical study in Table 1. In a randomized, sham-surgery-controlled trial [22], overall clinical improvement was not significant at the cohort level, although patients 60 years of age or younger showed significantly greater improvement than the sham-surgery group, while older patients did not. In addition, dystonia and dyskinesia recurred in 15% of patients who received transplants despite reduction of dopaminergic medication. This result shows variability in both therapeutic responses and adverse effects. This inconsistency was reinforced in a double-blind trial, placebo-controlled trial [23], where the primary endpoint was not met overall, although patients with milder baseline disease who received a larger graft showed significant improvement compared with placebo. More than half of the patients in this trial developed graft-induced dyskinesia, leading the authors to conclude that fetal nigral transplantation could not be recommended as a therapy for Parkinson's disease on the basis of these results. Long-term follow-up studies further illustrate this variability: in one report [24], two patients exhibited sustained motor improvement for up to 15–18 years after transplantation, including discontinuation of dopaminergic therapy, although graft-induced dyskinesia of mild-to-moderate severity persisted in both cases; such outcomes have not been consistently reproduced across the wider cohort from which these patients were drawn.

Together, these studies highlight the substantial variability and methodological limitations that continue to hinder the clinical translation of dopaminergic cell transplantation therapies in Parkinson's disease – variability that must be interpreted within each product's own evidence stream rather than compared across the fundamentally different fetal-tissue and stem-cell-derived technologies summarized in Table2.

Key challenges in clinical translation

The variability observed in clinical outcomes is not random but reflects underlying challenges in the design and implementation of dopaminergic cell transplantation. Several key factors contribute to this inconsistency, including incomplete dopaminergic identity of grafted cells, graft-induced dyskinesia, and limited functional recovery [13,14,25,26]. Understanding these challenges is essential for improving the clinical translation of cell-based therapies for Parkinson's disease.

Incomplete dopaminergic identity

One major challenge in clinical translation is the incomplete or incorrect dopaminergic identity of transplanted cells, which can limit therapeutic efficacy and lead to unpredictable outcomes [14,26,27]. Long-term graft survival remains a necessary

Table 2: Summary of Clinical Trials Evaluating Cell Transplantation Therapies for Parkinson's Disease

Study	Study Design	Main Findings	Major Limitations
Sawamoto *et al*., 2025 (Allogeneic, HLA-matched iPSC-derived) [20]	Open-label Phase I/II trial, n=7	Substantial patient-level variability: 3 of 6 evaluable patients improved 32.4-50.0% in MDS-UPDRS Part III "off" score at 24 months, a 4th improved 9.1%, and 2 showed no improvement (mean change 20.4%)	No control group, small sample size, non-randomized design, open-label design
Schweitzer *et al*., 2020 (Autologous iPSC-derived) [21]	First-in-human iPSC-derived cell transplantation case study	Modest improvement over 18-24 months	Single-patient study without criteria
Freed *et al*., 2001 (Fetal ventral mesencephalon) [22]	Randomized controlled fetal mesencephalic transplantation trial	Benefit observed in a subset of younger patients; graft-induced dyskinesia reported	Primary outcome not significant; benefit limited to a post-hoc age subgroup (60 yr); dyskinesia in 15% of recipients
Olanow *et al*., 2003 (Fetal ventral mesencephalon) [23]	Double-blind controlled transplantation trial	Limited motor improvement in only a subset of patients	Primary endpoint not achieved; graft-induced dyskinesia
Kefalopoulou *et al*., 2014 (Fetal ventral mesencephalon) [24]	Long-term follow-up study	Sustained motor improvement reported for 15-18 years in select patients	Small sample (two case reports, n=2); persistent graft-induced dyskinesia in both patients; findings not generalizable to the broader treated cohort

foundation for clinical benefit, but survival alone is not sufficient. Grafted cells must also develop into the specific subtype of midbrain dopaminergic neuron required for stable and functional recovery, so both durable graft survival and correct dopaminergic subtype specification are critical determinants of transplantation success. Cells that express dopaminergic markers may appear successful, even when they are only partially specified or not fully equivalent to authentic nigral dopaminergic neurons. Authentic nigral (A9-subtype) identity requires coordinated expression of a defined transcription-factor and membrane-marker profile – including FOXA2, NURR1 (NR4A2), PITX3, the dopamine transporter (SLC6A3/DAT), the A9-specific marker ALDH1A1, and the potassium channel GIRK2 – together with functional maturation such as autonomous pacemaking activity and physiological synaptic integration into host circuit [14]. Expression of tyrosine hydroxylase alone, without this fuller molecular and functional profile, does not establish complete dopaminergic specification. This distinction is often overlooked in preclinical studies, where partial dopaminergic identity may still be sufficient to produce apparent therapeutic benefit. In many animal models, outcomes are evaluated using relatively simple behavioral readouts, such as rotational improvement, which can be rescued by limited dopamine release without requiring precise reconstruction of the nigrostriatal pathway. In addition, the amphetamine-induced rotation test commonly used to assess these grafts in preclinical study is a crude, insensitive measure of dopaminergic function, allowing grafts with incomplete identity to generate measurable improvement (the smaller scale and lower circuit complexity of rodent brains reduce the need for strict subtype specificity, allowing grafts with incomplete identity to generate measurable improvement). The much shorter distance grafted axons must travel to reinnervate the rodent striatum, roughly a tenth of the length of the human nigrostriatal pathway, further contributes to this apparent tolerance, as even a graft with heterogeneous or incompletely specified identity can achieve more extensive functional coverage within the smaller rodent target field [28]. Moreover, the short duration of most preclinical studies further contributes to this issue, as early motor recovery may be observed within weeks to months without capturing long-term instability or off-target effects.

In clinical settings, however, partial dopaminergic identity is not sufficient. Parkinson's disease in human patients involves greater biological complexity and requires long-term stability of graft function. Therapeutic success depends not only on dopamine production, but on whether transplanted cells represent the correct dopaminergic subtype and maintain that identity over time. Cells with incomplete or incorrect specification may survive transplantation and produce initial symptomatic improvement, but fail to provide precise and durable functional recovery.

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Moreover, incorrect dopaminergic identity can lead to off-target neuronal differentiation and heterogeneous graft composition. For example, cells that express tyrosine hydroxylase (TH) may not necessarily belong to the intended midbrain dopaminergic lineage, as TH is also present in other catecholaminergic neurons. As a result, reliance on TH expression alone is insufficient to confirm correct dopaminergic identity. In addition, insufficiently controlled differentiation can result in the presence of unintended neuronal populations, including serotonergic cells, which can disrupt normal dopamine signaling and contribute to abnormal motor outcomes. These factors highlight that accurate and stable dopaminergic identity is essential for achieving consistent and reliable clinical outcomes.

Graft-induced dyskinesia

Graft-induced dyskinesia (GID) refers to involuntary, dyskinesia-like movements that appear in a subset of patients after dopaminergic cell transplantation[26]. GID is distinct from levodopa-induced dyskinesia (LID). LID occurs during periods when dopaminergic medication is active and would be expected to resolve if medication were stopped. GID, however, can remain even when patients are off all anti-parkinsonism medication. This indicates that GID arises from the graft itself rather than from exogenous dopamine. GID was first identified as a distinct clinical entity in the earliest double-blind, placebo-controlled fetal transplantation trials[22,23]. It affected 13 of 23 patients in one trial and 5 of 33 in another. Clinically, GID can be substantially disabling. It can also offset the motor benefit the graft was intended to provide. For this reason, GID should be understood as a significant clinical complication.

Rather than representing an isolated adverse effect, GID suggests that the graft has failed to reproduce the spatial and temporal precision of physiological nigrostriatal signaling. Dopamine neurons normally project to specific striatal circuits, and dopamine release is shaped by neuronal firing patterns in a phasic, activity-dependent manner[2,29]. A graft that does not reproduce this pattern may instead generate diffuse or poorly timed dopamine release. Supporting this, PET and SPECT imaging performed more than a decade after fetal graft transplantation in a Parkinson's disease patient revealed an elevated striatal serotonin-to-dopamine transporter ratio, indicating that dopamine was being taken up by serotonergic graft terminals and released as a false transmitter rather than through normal dopaminergic reuptake and release[13]. Treatment with a serotonin 5-HT1A agonist, which suppresses serotonin neuron activity, significantly reduced this patient's dyskinesia severity without changing motor scores, arguing against a simple loss of dopamine tone as the explanation. These findings show that dysregulated, non-physiological dopamine release can contribute to GID, though this specific mechanism has not been confirmed across a broader patient population.

Graft composition is another proposed contributor to GID risk, specifically the presence of serotonergic neurons alongside dopaminergic cells. Since serotonin neurons develop close to dopamine neurons in the ventral mesencephalon, they are often included unintentionally in fetal tissue grafts. Serotonergic neurons can take up dopamine and store it, but they lack the autoregulatory mechanisms of authentic dopaminergic neurons, so this dopamine may be released away from its intended synaptic targets. In animal models, a 5-HT1A receptor agonist that suppresses serotonin neuron activity reduces GID, and serotonin-rich grafts worsen dyskinesia more than dopamine-rich grafts[30]. However, serotonin content does not appear to be a necessary cause of GID. In a separate rodent study using stem-cell-derived dopaminergic grafts, spontaneous GID developed in animals whose grafts contained no detectable serotonin neurons at all. In that study, dyskinesia was reduced by dopamine D2 receptor antagonists, not by serotonin receptor agents, and its severity correlated with the number of dopaminergic cells in the graft and the degree of microglial activation[31]. Together, these findings suggest that serotonergic graft composition can contribute to GID in some contexts but is not its only cause, and that dopaminergic cell number and neuroinflammatory response should be considered alongside it.

Graft dose has also been proposed as a contributing factor. Insufficient graft size is a plausible cause of poor outcomes. Several reviews list graft size, along with placement and other surgical variables, among the factors associated with GID risk[30], and one rodent study found that dyskinetic animals had significantly more dopaminergic (TH-positive) cells in their grafts than non-dyskinetic animals, with dyskinesia severity correlating with this cell count[31]. However, the only controlled dose-response study available found no adverse effect of higher doses. Rats given low, high, or maximum feasible doses of dopaminergic cells all achieved full functional recovery, with only the lowest dose showing delayed recovery[32]. This result should be interpreted cautiously, though, since it relied on the amphetamine-induced rotation test, which plateaus at high turning rates and cannot reliably detect dose-dependent differences in graft size or reinnervation[33]. Whether excessive graft size contributes to GID in humans therefore remains an open question.

Importantly, GID is likely underrepresented in animal models. One reason for this is that spontaneous, unprovoked dyskinesia — the presentation that defines GID during ”off” periods in patients — has been reliably reproduced in only one rodent model and has never been observed in the standard primate model, so most studies instead rely on drug-induced movements as an imperfect proxy for the human phenotype[26]. Another reason is that many preclinical studies use short obser-

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vation periods, while GID may emerge late over longer timelines: most studies assess outcomes within 18-24 weeks post-transplantation, but spontaneous GID in rats was not observed until 30 or more weeks after grafting[26,31]. Moreover, animal models typically involve simplified lesions, controlled experimental conditions, and relatively purified graft populations that do not capture the full heterogeneity of clinical transplantation[34]. These factors may holistically underestimate the variability and design-related risks present in clinical transplantation

Limited functional recovery

Even when transplanted cells survive and exhibit dopaminergic characteristics, functional recovery of patients often remains partial, variable, and inconsistent[35]. This limitation likely reflects the combined effects of the previously discussed challenges in dopaminergic transplantation. Incomplete dopaminergic identity can result in grafts that do not possess the specificity required for stable and functional recovery, while dysregulated or imprecise dopamine signaling can interfere with, rather than restore, normal neural circuit activity[25]. Accordingly, transplanted grafts may produce a limited degree of symptomatic improvement, but still fail to achieve reliable and durable restoration of motor function in human patients. This suggests that graft survival or mere dopamine production alone cannot be considered sufficient indicators of transplantation success. Instead, successful clinical outcomes require not only graft survival and dopaminergic function, but also precise cellular identity and physiologically regulated integration into host neural circuits[36].

Discussion

This study considers design-related limitations as a contributor to the variability observed in clinical outcomes of dopaminergic cell transplantation, in addition to broader biological unpredictability and clinical and procedural differences across trials, such as patient selection and disease stage, that were not evaluated here. The failure modes identified throughout this are not isolated complications. They reflect systematic gaps between what is considered successful in preclinical models and what is actually required for reliable clinical translation in human patients.

The failure modes discussed in this report suggest a common underlying issue in the current design of dopaminergic transplantation. Here, the failure modes are the three challenges introduced above: incomplete dopaminergic identity, GID, and limited functional recovery. In turn, the current design of dopaminergic transplantation refers to the differentiation protocol and graft composition choices that give rise to them. Incomplete dopaminergic identity can produce grafts that lack the specificity necessary for stable and functionally appropriate recovery, while dysregulated or imprecise dopamine signaling can further disrupt host neural circuit activity rather than restore normal physiological control. Significantly, these factors do not act independently, but interact with one another to generate grafts that may appear functional in simplified preclinical settings while failing to achieve consistent and durable performance in complex clinical conditions. As a result, clinical outcomes become variable, with both therapeutic benefit and adverse effects differing across patients.

These findings suggest that improving the clinical translation of dopaminergic cell transplantation will require a shift in how transplantation success is defined and evaluated. Rather than relying primarily on graft survival or marker expression, future strategies should focus more strongly on functional design principles that are directly relevant to clinical outcomes. In particular, future transplantation approaches should prioritize precise specification of dopaminergic cell identity and tighter control over graft composition, goals that recent work described below has already begun to advance[37,38]. Achieving physiologically regulated signaling within the host neural circuits, meaning control driven by the circuit's own activity rather than applied from outside, remains largely theoretical objective at this stage, because grafted neurons take months to years to integrate into host circuitry and even basic restoration of striatal dopamine release has yet to be consistently demonstrated[39]. Preclinical animal studies remain essential for establishing safety and an early signal of efficacy before a strategy applies to patients. At the same time, graft evaluation in these studies should also include longer-term and more functionally relevant criteria, since short-term improvements observed in simplified animal models do not fully capture how a graft is likely to perform under real clinical conditions[40].

Although several challenges still remain, recent work has begun to address some of them. On the differentiation side, Kim *et al.* (2026)[37] added a growth factor and a WNT inhibitor to an existing differentiation protocol. In culture, this almost tripled the yield of mature dopamine neurons and reduced unwanted off-target cell types from 22% to 8%. After transplantation, grafts made with the new protocol contained more dopamine neurons overall (46% to 82% of graft cells) and an eight-fold increase in the authentic A9 subtype specifically (3.3% to 26%). Animals that received these grafts were also the only group to show significant recovery on a fine motor task. As with the preclinical studies discussed above, however, this recovery was observed in the acute, toxin-induced 6-ODHA model instead of in progressive human disease, so the same translational caveat still applies. Separately, Park *et al.* (2026)[38] describe two advances in graft engineering: sorting cells by a fluorescent marker before implantation to enrich for dopamine neurons and remove off-target cells, and a screen that identified a pathway driving cell death after

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grafting. Targeting that pathway with an already-approved anti-inflammatory drug, given alongside the graft, significantly improved both neuron survival and behavioral recovery in a Parkinson's disease mouse model. On the functional-assessment side, new tools let graft activity be turned up or down after implantation without surgery, enabling to fine-tune graft signaling instead of relying on a fixed dose. If the limitations described in this investigation are truly design-related, refining and combining these strategies (better-specified cells, engineered survival and purity, and tunable post-implantation control) may help close the gaps described throughout this investigation.

Conclusion

Dopaminergic cell transplantation has shown consistent success in animal models, yet its clinical translation in patients with Parkinson's disease remains inconsistent. This report points to design-related limitations, alongside broader biological unpredictability and unevaluated clinical factors such as patient selection and disease stage, as a plausible contributor to this translational gap. In particular, incomplete dopaminergic identity, dysregulated dopamine signaling, and the resulting variability in functional recovery reveal that graft survival or apparent dopaminergic characteristics alone are not sufficient to define transplantation success in clinical settings. Instead, successful clinical translation requires more precise, functionally informed, and biologically controlled approaches that are capable of meeting the greater complexity in human Parkinson's disease.

Despite these challenges, continued advances in stem cell differentiation, graft design, and methods of functional evaluation provide an important path forward. As these translational limitations become better understood and more effectively addressed, dopaminergic cell transplantation may be further developed into a more consistent, reliable, and clinically meaningful therapeutic strategy for Parkinson's disease.

Acknowledgments

Thank you for the guidance of my mentor, Sujin Kim, from Johns Hopkins University in the development of this research paper.

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