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Stem Cell Therapy in Parkinson's Disease

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ABSTRACT

Parkinson's disease is one of the most prevalent neurodegenerative disorders globally, with its incidence on the rise owing to population aging. Presently, the therapies accessible for Parkinson's disease lack disease-modifying capabilities and are encumbered by various limitations as outlined in this review. Currently, no cure exists for PD and, treatment approaches primarily aim at managing symptoms by reinstating dopaminergic activity. Nonetheless, cell replacement therapies offer promise as midbrain dopaminergic neurons have demonstrated the ability to replenish dopaminergic neurotransmission and functionally rehabilitate the dopamine-deficient striatum. We particularly delve into the potential applications of stem cells in PD treatment and explore how stem cell investigations have enriched our understanding of the condition. Stem cells offer immense potential for regenerative medicine as they have the capacity for unlimited expansion, generating large quantities of specialized cells essential for transplantation. Derived from fetal sources, embryonic origins (embryonic stem cells or ESCs), or reprogrammed from adult cells (induced pluripotent stem cells or iPSCs), stem cells possess the unique ability to differentiate into specific cell types relevant for clinical applications and mature into functional cells in vivo. While transplanting fetal or ESC-derived tissues often triggers an immune response, autologous transplantation using iPSCs derived from one's own cells eliminates the risk of rejection and reduces the need for immunosuppression. Nevertheless, despite these advantages, cell therapy encounters significant challenges that researchers are striving to address. This review will explore the steps necessary to ensure the safety, effectiveness, and clinical feasibility of cell replacement therapy, focusing particularly on its application in neurodegenerative diseases like Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) stands as the second most prevalent neurodegenerative condition, impacting almost 2% of individuals aged 65 and above. It entails a gradual decline in dopaminergic neurons within the substantia nigra, leading to various motor symptoms such as tremors, stiffness and slow movements (bradykinesia)[1].Additionally, patients may experience postural instability as the disease advances**.** Parkinson's disease (PD) is a neurological disorder characterized by movement difficulties, mental health challenges, sleep disturbances, pain, and various other health concerns. It progresses gradually over time and currently lacks a cure, though treatments and medications can help alleviate symptoms. Typical manifestations include tremors, muscle stiffness leading to painful contractions, and speech difficulties. PD often leads to significant disability and a necessity for care, with a substantial number of individuals developing dementia as well. While more commonly seen in older individuals, PD can also affect younger people, with men being disproportionately affected compared to women. The exact cause of Parkinson's disease (PD) remains unidentified, but individuals with a family history of the condition face a heightened risk. Additionally, exposure to factors such as air pollution, pesticides, and solvents may elevate the risk of developing PD. Symptoms of Parkinson's disease worsen progressively, significantly impacting overall well-being and quality of life. Motor symptoms include slow movement, tremors, involuntary movements, rigidity, difficulty walking, and imbalance. Non-motor symptoms encompass cognitive impairment, mental health disorders, dementia, sleep disturbances, pain, and sensory disturbances. Involuntary movements (dyskinesia) and painful muscle contractions (dystonia's) can impede speech and mobility, contributing to high disability rates and the need for care. Many PD patients also experience dementia as the disease advances. While Parkinson's disease stands as the most prevalent movement disorder, others like multiple system atrophy, progressive supra nuclear palsy, chorea, ataxia, and dystonia exist. Some share similar symptoms with PD such as tremors, slow movement, and rigidity. These disorders face comparable challenges in diagnosis, treatment gaps, and medication access, particularly in low- and middle-income countries (LMIC). The average age of Parkinson's disease (PD) onset is 55 years, with aging being the primary risk factor for its development. Roughly 10% of PD patients experience young-onset PD, diagnosed between 21 and 50 years of age, often with a higher likelihood of familial or genetic factors. In contrast, later-onset PD typically affects individuals over 70 years of age [2]. The precise cause of Parkinson's disease (PD) remains elusive. However, advancing age is identified as

the primary risk factor. Aging can trigger a series of stressors in the Substantial nigra (SN), leading to neuronal weakening and reduced responsiveness to further insults. Both environmental and genetic factors play roles in influencing the risk and progression of the disease. Genetic factors account for only about 10% of PD cases directly. Environmental factors such as vascular brain damage, repetitive head injuries, neuroleptic medications, pesticide exposure, smoking, caffeine consumption, and manganese toxicity have all been associated with an increased risk of developing Parkinsonism [3]. Another notable aspect of PD is the presence of Levy Bodies (LB), which consist of Misfiled aggregates of the α-syncline (α-sync) protein. The transmission of α-sync aggregates from neuron to neuron contributes to the decline of dopaminergic neurons in the substantial nigra (SN). These neurons are vital for inter-neuronal communication as they produce and release dopamine, a neurotransmitter crucial for regulating brain communication and movement. In PD, the compromised functionality of dopaminergic neurons directly affects their role in transmitting signals to the basal ganglia, a brain region involved in initiating and regulating movement patterns. Often, patients remain asymptomatic and undiagnosed until approximately 80% of dopamine neurons are lost, leading to symptoms like tremors, slow movement, stiffness, and balance issues. Consequently, the disruption in dopamine transmission impairs the normal functioning of the basal ganglia, resulting in difficulties coordinating and controlling movement. The development of therapies aimed at halting Neurode generation and preserving dopaminergic neurons is crucial for enhancing the quality of life for individuals with PD [4].

ETIOLOGY OF PARKINSON'S DISEASE

Parkinson's disease (PD) is a complex condition influenced by a combination of genetic and environmental factors. Aging stands out as the predominant risk factor, with the median age of onset typically around 60 years. As individuals age, the incidence of PD increases significantly, reaching 93.1 cases per 100,000 person-years in the age group of 70 to 79 years. Moreover, there are notable cross-cultural differences in PD prevalence, with higher rates observed in regions such as Europe, North America, and South America compared to African, Asian, and Arabic countries.

1. CIGARETTE SMOKING

Extensive research has delved into the relationship between cigarette smoking and Parkinson's Disease (PD), yielding largely consistent findings. Numerous epidemiological

studies, primarily case-control investigations, demonstrate a decreased risk of developing PD among smokers, a trend supported by larger cohort studies as well. A comprehensive meta-analysis encompassing 44 case-control studies and 8 cohort studies from 20 countries highlighted an inverse association between smoking and PD, with a pooled relative risk of 0.39 for current smokers. Two additional meta-analyses echoed this inverse correlation, revealing pooled odds ratios ranging from 0.23 to 0.70, indicative of a protective effect against PD. Furthermore, these analyses noted a negative correlation between the duration and intensity of smoking and PD risk, suggesting a significant reduction in risk among heavy or long-term smokers compared to non-smokers.

The precise mechanisms underpinning this diminished risk remain incompletely understood. Experimental models of PD indicate that activation of nicotinic acetylcholine receptors on dopaminergic neurons by nicotine or selective agonists exerts Neuro protective effects. However, nicotine's ability to stimulate dopamine release, integral to reward mechanisms, complicates interpretation regarding whether smoking truly mitigates PD risk or if PD diminishes the inclination towards smoking. Notably, individuals with PD, due to reduced dopamine levels, may exhibit lower susceptibility to addictive behaviors and therefore smoke less. This notion finds support in observations that individuals with prodromal PD and PD find it comparatively easier to quit smoking than controls, suggesting decreased responsiveness to nicotine as a contributing factor to this association [5].

2. CAFFEINE

Numerous studies have explored the impact of caffeine consumption on Parkinson's disease (PD) development, consistently revealing a decreased risk among coffee drinkers. Caffeine, acting as an adenosine A2A receptor antagonist, is believed to offer protection against PD and has demonstrated neuro protective effects in mouse models of the disease. Previous findings suggest a 25% risk reduction in PD development among coffee consumers. Large-scale prospective epidemiological investigations, alongside multiple retrospective studies, further support this notion, with coffee drinkers exhibiting a relative risk ranging from 0.45 to 0.80 compared to non-drinkers. A meta-analysis encompassing case-control and cohort studies confirms a significantly lowered risk of PD in coffee drinkers (RR 0.69). Moreover, regular tea consumption has also been associated with a reduced PD risk. However, similar to smoking, the precise causal role of caffeine in PD prevention remains uncertain. Variations in study outcomes have been observed, particularly concerning gender. While two cohort

studies highlight a robust inverse correlation between coffee consumption and PD risk in men, this association appears weaker in women. Notably, among post-menopausal women, the impact of caffeine is influenced by hormone replacement therapy, specifically estrogen intake. As estrogen competes with caffeine metabolism, interactions between these substances may partially account for the dependence of PD risk on hormone replacement therapy in post-menopausal women.

3. PESTICIDES, HERBICIDES AND HEAVY METALS

In 1983, the discovery of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) as a contributor to nigro striat degeneration emerged when individuals exhibited typical Parkinson's disease (PD) symptoms after self-injecting a drug tainted with MPTP. MPTP metabolizes into the neurotoxin MPP+ (1-methyl-4-phenylpyridinium), a mitochondrial complex-I inhibitor that selectively harms dopaminergic cells in the substantial nigra. This identification linked environmental toxins to the potential cause of PD. Subsequent research has revealed associations between pesticide exposure and PD, with one study indicating a heightened risk in men with professional pesticide exposure and late-onset PD (odds ratio [OR] 2.2). Parquet, a herbicide structurally akin to MPP+, and rotenone, a pesticide, similarly act as selective complex-I inhibitors and induce dopaminergic loss in PD animal models. Other epidemiological investigations have explored the relationship between exposure to these chemicals and PD risk, along with surrogate markers like farming, well water consumption, and rural residency. Welding and heavy metal exposure, including iron, copper, lead, aluminum, and zinc, have also been scrutinized, yet their connection with PD remains uncertain.

4. GENETICS

While Parkinson's disease (PD) typically arises without a known cause, a minority of cases (10–15%) report a family history, with around 5% demonstrating Mend Elian inheritance. Additionally, an individual's susceptibility to PD is influenced by partly undefined polygenic risk factors. Genes associated with PD are labeled with a "PARK" designation according to their discovery sequence. Presently, 23 PARK genes have been linked to PD. Some of these genes' involvement in PD remains uncertain (PARK5, PARK11, PARK13, PARK18, PARK21, and PARK23), while others are considered risk factors (PARK3, PARK10, PARK12, PARK16, and PARK22). The most significant genetic risk factors for PD include mutations in GBA1, which encodes β-glucocerebrosidase, a lysosome enzyme crucial for

glucocerebroside hydrolysis. GBA1 mutations are associated with gauche disease, the most prevalent lysosome storage disorder. Other genetic risk factors encompass the major histocompatibility complex, class II (HLA-DQB1), and the tau protein-encoding gene MAPT, among others.

5. AUTOSOMAL DOMINANT PD

The initial form of familial Parkinson's Disease (PD), stemming from a point mutation in the α-syncline gene (SNCA), was identified in 1997. Subsequently, four additional point mutations, as well as gene duplication or triplication, have been associated with autosomal dominant PD. Nevertheless, these mutations are relatively uncommon. The most prevalent form of autosomal dominant monogenic PD arises from mutations in the gene encoding leucine-rich repeat kinase 2 (LRRK2). Six LRRK2 mutations have been recognized as pathogenic, with the p.G2019S mutation being the most prevalent, estimated to contribute to 1% of sporadic and 4% of familial PD cases worldwide. Recent genetic investigations have led to the identification of further mutations in other genes responsible for autosomal dominant PD.

6. AUTOSOMAL RECESSIVE PD

Autosomal recessive forms of Parkinson's disease (PD) typically manifest at an earlier age compared to classical PD. Three PARK-designated genes associated with autosomal recessive PD are implicated in mitochondrial homeostasis (PRKN, PINK1, and DJ-1). Notably, both PINK1 and parkin (encoded by the PRKN gene) participate in the same mitochondrial quality control pathway, wherein PINK1 recruits parkin to malfunctioning mitochondria, initiating mitophagy. Mutations in PRKN represent the most common cause of autosomal recessive familial PD, accounting for up to 50% of all early-onset cases. Additionally, several autosomal recessive genes have been linked to atypical Parkinsonism, exhibiting variable features.

PATHOGENESIS OF PARKINSON DISEASE

Several mechanisms have been implicated in the pathogenesis of Parkinson's disease (PD), with the aggregation of α-syncline considered central to disease development. Additionally, other processes such as abnormal protein clearance, mitochondrial dysfunction, and neuro inflammation are believed to contribute to the onset and progression of PD. However, the precise relationship between these pathways remains uncertain.

α-SYNCLINE MISFOLDING AND AGGREGATION

In its natural state within the brain, α-syncline typically lacks a specific tertiary structure, appearing mostly unfolded. However, in aqueous environments, it may form stable tetramers that exhibit resistance to aggregation. Various forms of α-syncline are observed in the Parkinson's disease brain, encompassing unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils.

2. MITOCHONDRIAL DYSFUCTION

Mitochondrial dysfunction is recognized as a pivotal factor in the development of both idiopathic and familial Parkinson's disease (PD). Initial postmortem examinations of the substantial nigra pars compact (Snaps) in PD brains revealed a deficit in mitochondrial complex-I, a crucial component of the electron transport chain. These findings represented one of the initial direct associations between mitochondrial dysfunction and PD [5].

CURRENT TREATMENT OF PARKINON DISEASE

Significant advancements have been achieved in Parkinson's disease (PD) treatment over the last fifty years, yet levodopa remains the most effective medication for managing PD symptoms. Levodopa stands as the most effective drug for managing Parkinson's disease (PD) symptoms, especially those related to brady kinesia. However, due to the frequent occurrence of motor complications such as fluctuations and dyskinesia with levodopa therapy, there remains ongoing debate regarding the optimal timing to initiate this treatment in the course of PD. The inclusion of carbidopa, a peripheral dopa decarboxylase inhibitor, enhances the therapeutic effects of levodopa. For patients prone to peripheral side effects like nausea and vomiting, additional carbidopa may be supplemented alongside the standard carbidopa/levodopa preparation.[6] It's crucial to note that while many Parkinson's disease (PD) treatments primarily target motor symptoms, the condition often entails additional non-motor symptoms. On one hand, there are neurological issues linked to the emotional toll of PD, including apathy, anxiety, and depression. On the other hand, there are symptoms stemming from the adverse effects of dopaminergic therapy, such as addiction or nocturnal hyperactivity. However, most non-motor symptoms do not improve with standard therapies and may even emerge or worsen with their initiation. These symptoms often arise early in the disease progression, underscoring the importance of their treatment. Furthermore, these symptoms can manifest even before motor symptoms, suggesting they are also linked to

dopamine deficiency. However, treatment for these symptoms is not specific to PD, as it aligns with approaches used in the general population. The current pharmacological approach primarily focuses on restoring dopamine levels, with Levodopa recognized as the primary treatment option. This dopamine precursor has been a significant breakthrough in managing Parkinson's disease (PD), reducing motor symptoms and enhancing patients' quality of life. Its success prompted exploration into other dopaminergic therapies. However, Levodopa administration is limited by the occurrence of adverse reactions, with dyskinesia being a major complication. Additionally, as the disease progresses, patients become less responsive to dopaminergic medication and necessitate higher and more frequent doses. To address these challenges, current formulations of Levodopa include decarboxylase inhibitors, like Carbidopa or Benserazide, which prevent peripheral dopamine metabolism, thus enhancing drug bioavailability. Simultaneous administration of Levodopa with other drugs is recommended to mitigate complications associated with high doses of a single medication. These drugs include rasagiline, sulfonamide, selegiline, and Monoamine oxidase B (MAOB) inhibitors, which elevate dopamine levels. Catechol-O-methyltransferase (COMT) inhibitors, such as entacapone and tolcapone, stabilize dopamine levels and alleviate motor complications by enhancing Levodopa absorption in the gastrointestinal tract, where most of this enzyme is located.

Another category of medications includes dopamine agonists like ropinirole and pramipexole, which have demonstrated safety and efficacy both as mono-therapy and in combination with Levodopa. Notable drugs in this class include rotigotine, available in transdermal patches for continuous drug delivery, and apomorphine, used as a rescue treatment for patients experiencing motor fluctuations via injections or subcutaneous infusions.

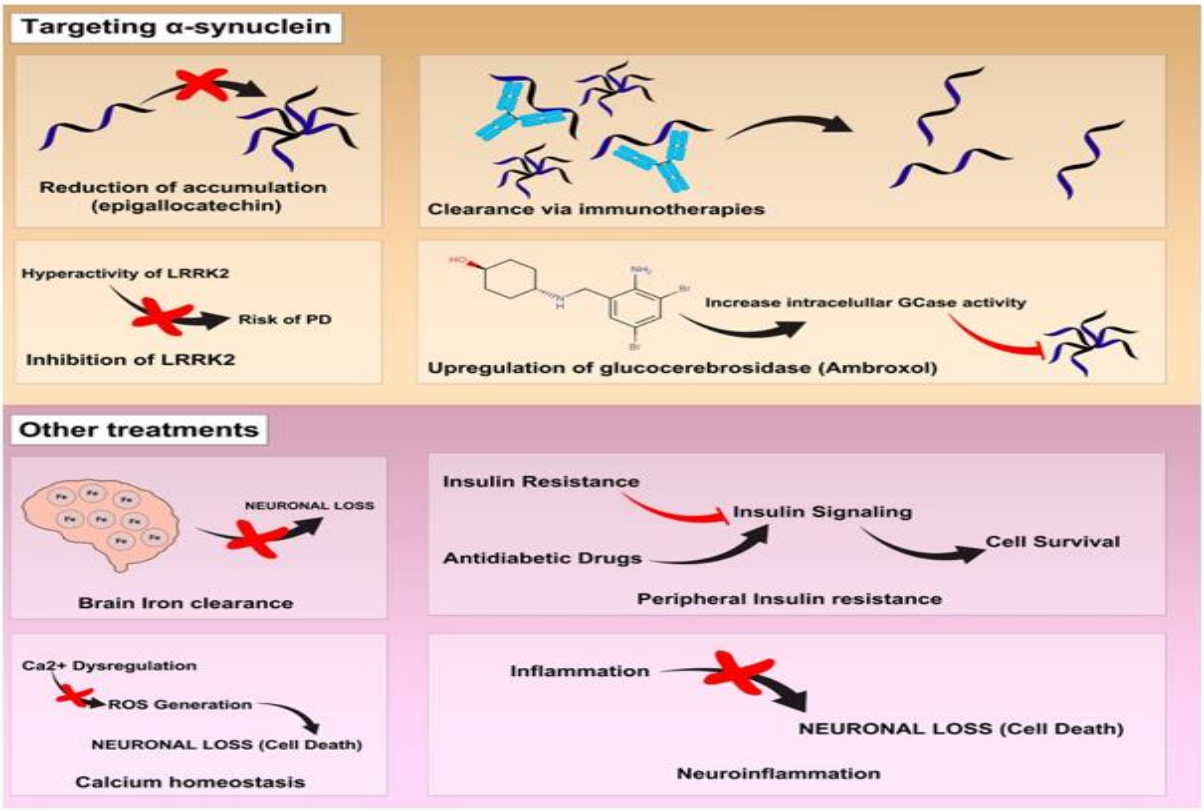

Fig 1. Current and emerging treatments of Parkinson's disease

Parkinson's disease (PD) lacks a curative treatment or any therapy capable of altering its progression. Therefore, the aim of treatment is to alleviate both motor and non-motor symptoms that arise throughout the disease's course. Currently, a variety of treatments are available to address the symptoms of PD. However, ongoing research is also exploring additional treatments to ascertain their therapeutic efficacy [fig1].

Chen et al. suggested in their study that certain autonomic symptoms like constipation, orthostatic hypotension, urinary dysfunction, erectile dysfunction, and pure autonomic failure could serve as prodromal dysautonomic markers for predicting and diagnosing PD due to their early onset and high prevalence among affected individuals. Therefore, patients with orthostatic hypotension can receive treatment with Fludrocortisone, Pyridostigmine, and Droxidopa. Urinary incontinence can be managed primarily with four types of drugs: Anticholinergic such as Darifenacin, Oxybutynin, Solifenacin, and Tolterodine; Beta-3-Agonists, with Mirabegron being the main option; Alpha-1A blockers including Alfuzosin, Silodosin, Tamsulosin, and Terazosin; and SNRIs like Duloxetine. Sialorrhea in Parkinson's patients, typically caused by slowed swallowing, can be addressed with Atropine drops, Botulin toxins A and B, Glycopyrrolate, or a Scopolamine patch. Additionally, digestive

issues such as constipation are initially managed with non-pharmacological approaches like dietary adjustments (e.g., consuming high-fibre foods and increasing fluid intake). However, if these measures prove ineffective, drugs such as Lubiprostone and Polyethylene glycol may be prescribed. For nausea and vomiting, commonly used treatment options include ondansetron and trimetho-benzamide [6].

Table 1. Drugs and its mechanism of action

DRUG	MECHANISM OF ACTION
Levodopa	Levodopa is utilized in the management of Parkinson's disease to address dopamine deficiency by supplementing its levels. However, extended administration may result in dyskinesia, attributed to the degeneration of dopaminergic neurons, alterations in white matter, and elevated astroglia levels within the striatum.
MAO Inhibitors	MAO-B inhibitors employed for Parkinson's disease offer symptomatic relief and may provide neuro protective effects. Safinamide, in addition to its MAO-B inhibition, also suppresses glutamate release. However, selegiline's relevance has diminished due to its interaction issues.
COMT Inhibitors	COMT inhibitors such as entacapone, tolcapone, and opicapone inhibit the COMT enzyme, resulting in increased levodopa levels in the blood by preventing peripheral degradation to 3-OMD.
NMDA receptor	Amantadine, an NMDA receptor antagonist, is used in Parkinson's disease to treat l DOPA-induced dyskinesia via altering glutamatergic neurotransmission.
	Carbidopa, like Amantadine, inhibits T cell

Carbidopa	activation and autoimmunity in Parkinson's disease by preventing levodopa conversion outside the CNS, implying a possible therapeutic role in lowering T cell-mediated diseases.
Zonisamide	Zonisamide may act in Parkinson's disease by inhibiting MAO-B, blocking T-type calcium channels, modulating dopamine metabolism, and providing neuroprotection via a variety of pathways.
Istradefylline	Istradefylline functions as an adenosine A2A receptor antagonist, enhancing dopamine-sensitive motor behavior in Parkinson's disease patients with levodopa-related motor difficulties by lowering adenosine receptor effects.
Apomorphine	Apomorphine works as a multimodal medication in Parkinson's disease, interacting with dopamine, noradrenaline, and serotonin receptors, providing a more comprehensive therapeutic strategy than standard single-action drugs.

LIMITATIONS TO CURRENT THERAPY

Parkinson’s disease is a prevalent neurodegenerative condition worldwide, and its incidence is rising due to the aging population. Presently, available therapies lack disease-modifying effects and are subject to several limitations, as discussed in this review. A primary constraint is the limited concentration of drugs reaching the central nervous system following systemic administration. The presence of biological barriers, notably the blood-brain barrier (BBB), impedes efficient drug delivery to the brain, thus diminishing the potential therapeutic benefits. This review explores mechanisms of transport across the BBB and novel strategies to enhance drug permeation. These approaches encompass non-invasive methods like intranasal and intravitreal administration, as well as the utilization of nanotechnology-based solutions employing polymeric carriers for intravenous injection, oral absorption in the

intestine, or delivery via the dermal mucosa. Additionally, the review evaluates more invasive options such as intracranial injected hydrogels and implanted devices for localized drug delivery. It emphasizes the importance of coupling efforts to discover new therapeutic drugs halting neurodegenerative disease progression or reversing their course with the development of efficient drug delivery systems. Consequently, advancements in pharmacology, nanotechnologies, and biomaterials for regenerative medicine are imperative to effectively combat neurodegenerative diseases.

Levodopa and other dopaminergic medications significantly enhance motor symptoms and quality of life for individuals in the early stages of Parkinson's disease. However, once the initial period of improvement diminishes, typically after a few years of dopaminergic therapy, patients progressively experience more disability despite using increasingly complex combinations of available anti-parkinsonian treatments. Eventually, they encounter "dopa-resistant" motor symptoms such as speech impairment, abnormal posture, gait and balance issues, as well as "dopa-resistant" nonmotor signs including autonomic dysfunction, mood and cognitive impairment, sleep disturbances, and pain. Additionally, they may also contend with drug-related side effects, notably psychosis, motor fluctuations, and dyskinesias. Consequently, the existing anti-parkinsonian therapy falls short of being considered ideal in terms of both efficacy and safety.

INTRODUCTION TO STEM CELLS

Stem cells are undifferentiated cells found in the human body that possess the capacity to develop into various cell types within an organism and can self-renew. These cells are present in both embryos and adult tissues [7]. Stem cells are the fundamental components of an organism with the ability to continually grow and transform into various cell types while preserving their initial reservoir.

Stem cells possess distinctive capabilities for self-renewal and differentiation into diverse cell types, contributing to developmental, regenerative, and reparative functions within the body.

TYPES OF STEM CELL

Stem cells exhibit a spectrum of differentiation capacities, classified as totipotent, pluripotent, multipotent, oligopotent, and unipotent, sourced from a variety of origins such as bone marrow, amniotic cells, and adipose tissue.

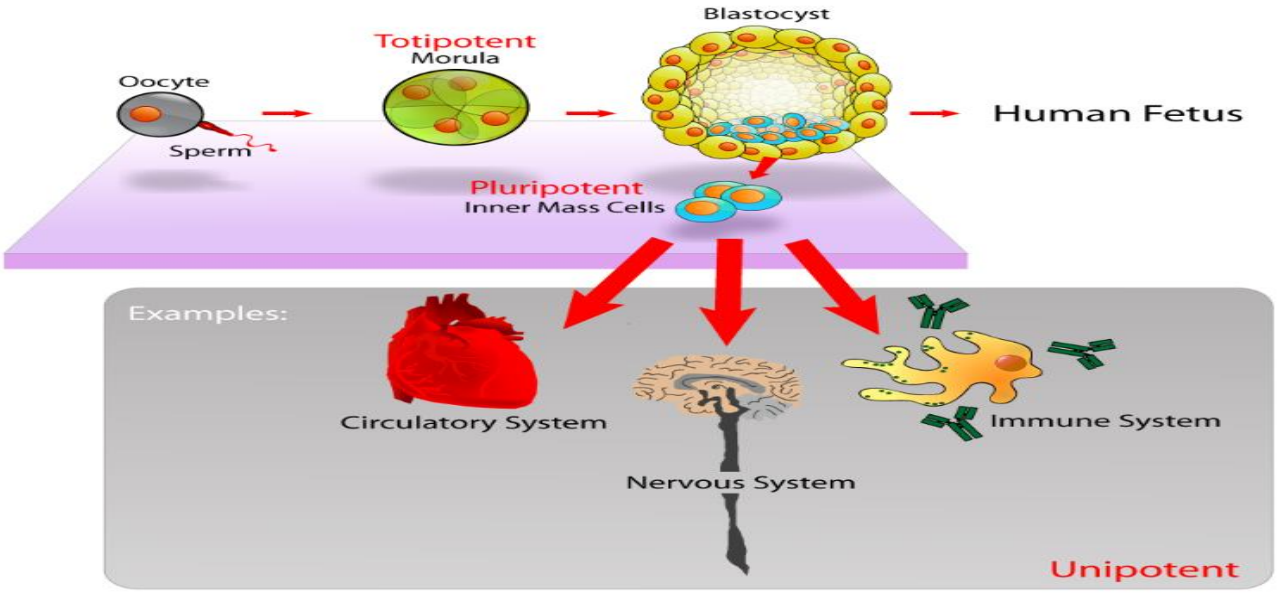

Fig 2. Types of stem cells

1. Totipotent stem cell

Totipotent stem cells (TSCs) possess the capability to mature into entire organisms, offering significant promise in fields such as regenerative medicine, mammalian breeding, and conservation efforts. Recent strides in induced pluripotent stem cell research have further enhanced these prospects.

2. Pluripotent stem cell

Pluripotent stem cells, such as human embryonic stem cells (hESCs), originate from the inner cell mass of embryos, presenting immense possibilities in areas like research, treatment, and industrial use.

3. Multipotent stem cell

Multipotent stem cells possess the capability to specialize into a single type of tissue within a specific germ line. They are pivotal in regenerative medicine as they generate distinct cell types within a particular lineage.

4. Oligopotent stem cell

Oligo-potent stem cells, present in adult organ tissues, have a limited capacity to specialize, restricted to specific cell lineages to which they are committed. This differs from multi-potent stem cells, which have broader differentiation abilities.

5. **Unipotent stem cell** Unipotent stem cells are a subtype of stem cell characterized by their capacity to differentiate exclusively into a single, specific cell type.

STEM CELLS THERAPY IN PARKINSON DISEASE

Clinical trials for Parkinson's disease (PD) using stem cell-based therapies are advancing swiftly. Numerous academic and industry initiatives are actively working to generate dopaminergic neurons from stem cells under conditions suitable for use in patients. In December 2015, a Phase I/IIa trial for PD utilizing a parthenogenetic stem cell source was announced, sparking considerable enthusiasm across traditional print media, social platforms, and particularly within the PD patient community. International Stem Cell Corporation (ISCO), headquartered in California, disclosed that its subsidiary Cyto Therapeutics had obtained approval from the Australian government to conduct a clinical trial involving 12 patients with moderate to severe PD at the Royal Melbourne Hospital in Melbourne, Australia. A subsequent press release indicated rapid progress in the program, with all patients scheduled for enrollment in the first quarter of 2016 and interim findings anticipated to be shared by October 2016. This milestone marks the first approval of a clinical trial utilizing pluripotent stem cells for PD treatment, garnering significant attention in the news. In the late 1970s and early 1980s, several research groups, building upon the pioneering work of Bjo¨rklund et al. and others, demonstrated that dopaminergic neurons obtained from the developing fetal midbrain (ventral mesencephalon – VM) could survive transplantation in animal models of PD. These transplanted cells not only endured in the adult striatum but were also capable of releasing dopamine, establishing connections with the host brain, and alleviating various motor and behavioral deficits in rodent models of PD, as outlined in reviews. Similar outcomes were observed when human fetal dopamine neurons were transplanted into the striatum of immunosuppressed rats. Encouraged by the collective success of studies in experimental animals across different research laboratories, numerous groups initiated open-label clinical trials in PD during the late 1980s and 1990s. The underlying rationale was to potentially replace the lost adult nigral dopamine cells in PD with grafted immature human dopaminergic neurons. While this approach cannot be considered a cure, it represents a promising strategy for treating the dopamine-responsive motor symptoms of PD by ensuring sustained physiological delivery of dopamine specifically targeted to the striatum.

In the recently announced ISCO trial, the company intends to transplant neural stem cells that have been differentiated from a pluripotent parthenogenetic cell line. These parthenogenetic cells are derived from unfertilized oocytes by inhibiting the second meiotic division, resulting in a pluripotent diploid cell line containing only maternal chromosomes. This sets them apart from other pluripotent cell sources like embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC), and their lack of paternal imprinting may pose unique challenges in their clinical adoption, potentially affecting their cell cycle and differentiation capacity. For transplantation, ISCO plans to utilize an expandable neural stem cell population derived from the parthenogenetic pluripotent cell source. According to published data, these cells are PAX6-positive, indicating a dorsal neural fate. However, genuine midbrain dopaminergic neurons stem from PAX6-negative ventral midbrain neural precursors. Consequently, the published data on the transplanted PAX6-positive neural stem cells do not demonstrate their ability to generate authentic midbrain dopaminergic neurons. Therefore, it remains uncertain how these cells could function in PD treatment, as they do not serve as replacement cells for the midbrain dopamine neurons that degenerate in this condition. The ability of stem cell-derived dopamine neurons to persist long-term, integrate into the host striatum, and recover lost brain function in the 6-hydroxydopamine (6-OHDA) lesion rat PD model is crucial for their advancement towards clinical application. In studies involving human ES cell-derived midbrain dopamine neurons, two separate research teams have achieved outcomes meeting these criteria. In both instances, surviving transplants were observed months post-implantation, displaying signs of differentiation into midbrain dopamine cells, axonal growth, dopamine release, and restoration of motor deficits, all without indications of abnormal cellular proliferation or tumor formation. ISCO claimed in an April 2014 press release that their parthenogenetic stem cells exhibited efficacy in 18 MPTP-treated non-human primates, resulting in "significant improvement in the main Parkinson’s rating score." However, these data have not been publicly disclosed. Conversely, in a recent study, the only transplantation study the company has published thus far, they mention testing the cells in 10 rats and only 2 monkeys, presenting no functional recovery data in either species. Consequently, both the safety profile and proposed mode of action of the stem cells remain uncertain, especially as the published study concludes that "Most of the engrafted hpNSCs were dispersed from the graft site and remained undifferentiated." Given the absence of dopaminergic neurons in the grafts, the authors suggest that the cells might function through the secretion of growth factors like BDNF and GDNF [8]. While similar hypotheses have been proposed with cell-based therapies for PD, relying on trophic support to enhance endogenous dopaminergic

neuron function rather than replacement, such approaches have historically yielded poor outcomes in clinical trials without plausible mechanisms and supporting evidence. The publicly accessible preclinical safety and efficacy data do not warrant the initiation of clinical trials at this time. It is unclear whether additional preclinical safety and efficacy data have been submitted to regulatory bodies, but greater transparency regarding the preclinical evidence is strongly recommended [8].

STEM CELLS BASED TREATMENT

As our understanding of Parkinson's disease (PD) improves, various pathways have emerged as potential targets for treatment. While conventional therapies focus on alleviating symptomatic stages, recent genetic insights suggest the feasibility of preventive neuroprotective treatments to delay disease onset and progression in individuals at risk of PD. Alongside efforts to manage symptomatic PD, researchers are exploring stem cell therapies as a means of replacing diseased neurons or tissues.

Among these approaches, dopamine (DA) cell transplantation stands out as a promising strategy for cell replacement therapy. By transplanting midbrain DA neurons into the dopamine-depleted striatum, it is possible to restore dopamine neurotransmission and replace lost neurons in PD patients. Clinical trials have demonstrated promising results, showing that transplantation of fetal midbrain tissues relieved neurological symptoms and restored motor functions in PD patients. Midbrain DA neurons for striatal grafts can be sourced from various tissues, including fetal tissues, porcine fetal substantia nigra neurons, carotid body cells, and immature retinal cells. While the safety and efficacy of different cell replacement therapies require further investigation in human trials, they hold potential as part of future PD management strategies.

1. Fetal Ventral Mesencephalon Tissue

Fetal ventral mesencephalon (VM) contains various neuronal populations, including dopamine (DA) neurons of the substantia nigra (SN) and ventral tegmental (VT) areas, oculomotor neurons, and reticular neurons. Animal studies testing fetal VM cell transplantation have shown promising results in alleviating Parkinson's disease (PD) symptoms. In a European clinical trial led by TRANSEURO, fetal VM tissues were transplanted into 150 PD patients meeting specific criteria for neural grafting, such as younger-onset PD without significant levodopa-induced dyskinesia. Over a four-year period,

patients underwent clinical observation and regular assessment with positron emission tomography (PET) and magnetic resonance imaging (MRI) scans. These trials have set standards for preclinical and clinical evaluation, demonstrating the feasibility and efficacy of fetal cell therapy and providing guidelines for future cell-based therapies using induced pluripotent stem cell (iPSC)-derived DA neurons.

However, several technical challenges remain before fetal VM transplantation can be widely implemented in clinical practice. One major hurdle is the poor survival of grafted DA neurons and limited dopaminergic reinnervation in the host striatum. Strategies to address this issue include incorporating neurotrophic factors like brain-derived neurotrophic factor (BDNF) and cotrans plantation with neural or paraneural origins. Another challenge is the limited availability of human fetal tissues, along with variations in protocols and lack of standardization. Transplantation of cells other than authentic fetal VM DA neurons has failed to demonstrate essential properties such as robust survival, DA release, and clinical benefits. Additionally, immunosuppressant administration, such as cyclosporine, is necessary throughout the transplantation and observational period to prevent allograft-induced immune rejection. Alternative cell therapies using hypo-immunogenic cells like mesenchymal stem cells (MSCs) have been explored as well.

2. MSCs

MSCs have demonstrated therapeutic potential for various diseases, including Parkinson's disease (PD). Due to their low immunogenicity, minimal teratoma risk, ethical acceptability, and low tumorigenicity post-transplantation, clinical trials utilizing MSCs as a therapeutic intervention are ongoing. MSCs can be obtained from diverse sources such as bone marrow aspirate, adipose tissue, peripheral blood from adult tissues, and Wharton’s jelly of the umbilical cord from neonatal tissues. Human umbilical cord MSCs are particularly advantageous for therapeutic applications due to their multilineage differentiation capacity, autologous transplantation feasibility, easy procurement, and lack of ethical concerns.

Despite these advantages, transplanted human umbilical cord MSCs exhibit low survival rates in the host and may lead to vein-transplanted cells causing capillary embolization and uncontrolled cell division. Only a small fraction of transplanted human umbilical cord MSCs is typically detected in the target tissue. Nonetheless, MSCs from various sources have shown improvements in PD symptoms in animal models treated with 6-hydroxydopamine (6-OHDA), a neurotoxin that induces oxidative stress and neuroinflammation.

The therapeutic effects of MSCs in PD models appear to be mediated through the secretion of neurotrophic factors such as BDNF, glial cell line-derived neurotrophic factor, and nerve growth factor. These factors protect dopamine neurons from apoptosis, stimulate neurogenesis, and promote the survival of regenerated neurons. Additionally, MSCs exhibit immune-modulatory properties by inhibiting microglial activation through the secretion of immunosuppressive cytokines or direct cell-cell contact.

Under specific conditions, MSCs can differentiate into neuron-like cells and astrocytes. Interestingly, both neuronal-primed MSCs and undifferentiated MSCs have shown beneficial effects when transplanted into PD animal models, suggesting that their therapeutic mechanism may not solely rely on direct cell replacement. MSCs alleviate PD symptoms by exerting antiapoptotic, anti-inflammatory, and neuro-protective effects, even in models of α-synuclein-induced dopamine neuron degeneration. In such models, MSCs stabilize microtubule assembly, inhibit α-synuclein-induced tau phosphorylation, and facilitate the clearance of α-synuclein, ultimately promoting the survival of dopamine neurons [9].

3. *Pluripotent Stem Cell-Derived Neuron Progenitor Cells*

Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), offer a promising avenue for cell-based therapies due to their ability to differentiate into various cell types, including dopamine (DA)-producing neurons. iPSC-based therapies have garnered attention due to their similar differentiation potential to ESCs but with fewer ethical concerns. Human PSCs (hPSCs) hold significant potential for regenerative medicine, particularly in replenishing degenerated midbrain DA neurons associated with Parkinson's disease (PD).

Directed differentiation of hPSCs into specialized cell types, such as DA neurons, has been achieved using established protocols for both 2D and 3D cultures. These differentiation methods involve the inhibition of specific signaling pathways to promote the differentiation of hPSCs into floor plate (FP) cells, which serve as precursors to DA neurons. Subsequent maturation steps yield functional DA neurons capable of engraftment in vivo and functional recovery in animal models of PD.

Compared to human fetal DA neurons, midbrain DA neurons derived from hPSCs demonstrate comparable efficacy in restoring motor function in PD animal models. Long-term engraftment and survival of these transplanted cells are crucial for sustained therapeutic effects, with studies demonstrating survival of hESC-derived midbrain DA neurons for over

six months post-transplantation. Precise control over the activity of engrafted cells can be achieved through drug-dependent stimulation or inhibition, enabling tunable rescue of motor function in PD animal models.

One advantage of iPSC-based therapies is the potential for autologous transplantation, reducing concerns about immune rejection. Preclinical studies in nonhuman primates have shown promising results, with autologous iPSC-derived DA neurons improving motor impairment without the need for immunosuppression. Clinical trials using hESC/iPSC-derived cell products for PD treatment have commenced in several countries, with superior risk management compared to trials using other stem cell types.

In addition to PSCs, other stem cell types such as human amniotic epithelial stem cells (hAECs) are being investigated in clinical trials. These cells have shown potential in promoting neural cell survival and regeneration, synthesizing neurotropic factors, and releasing neurotransmitters, offering another avenue for PD treatment.

4. Advantages and Disadvantages of iPSC-Based Therapy

Cell-based treatments, including those involving Mesenchymal Stem Cells (MSCs), have undergone both preclinical and clinical testing, with numerous findings indicating their ability to rectify pathological conditions by substituting degenerated neurons with healthy ones. However, the duration of therapeutic effects may be limited due to the existence of endogenous pathological proteins that could impact the functionality of the transplanted cells. For instance, the transfer of α-syn between cells has been observed, leading to the gradual appearance of α-synuclein-containing Lewy bodies (LBs) in the transplanted neurons.

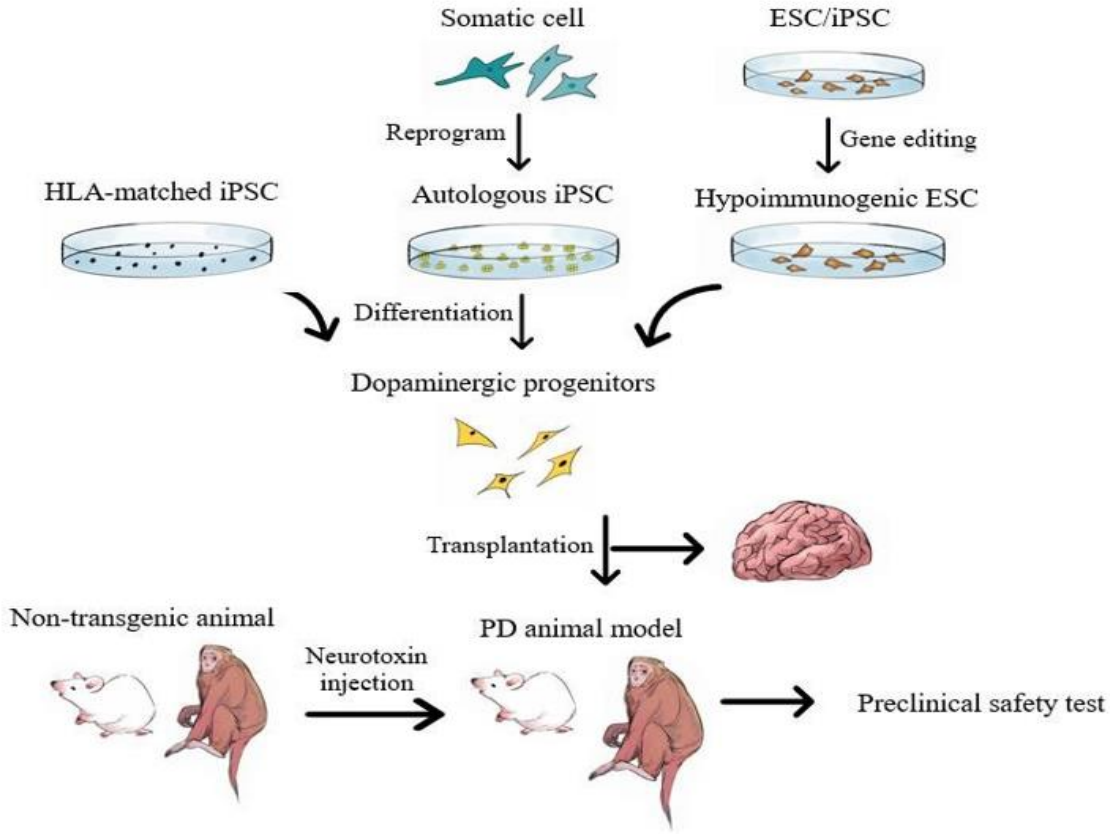

Fig 3. Stem cell therapy of Parkinson's disease

Both induced Pluripotent Stem Cell (iPSC) and Embryonic Stem Cell (ESC) derived Dopaminergic (DA) neurons exhibit the ability to survive post-grafting in animal models, extending axons that integrate into the brain and contribute to functional recovery from motor deficits induced by neurotoxins. As previously mentioned, generating autologous implants involves reprogramming the patient's fibroblasts to iPSCs, presenting a potential advantage of iPSC-derived cells over ESC-derived cells. Utilizing patient iPSC-derived neural grafting products eliminates the need for immunosuppression required for the survival of ESC-derived or fetal allografts.

However, the generation of a clinical-grade autologous iPSC line is time-consuming and costly, potentially requiring additional gene editing of the causative genes in patients with inherited familial PD. To address these challenges, the generation of hypoimmunogenic and universal iPSC lines from a "healthy" and well-characterized donor could be considered. Researchers have developed iPSC lines with inactivated major histocompatibility complex (MHC) class I and II genes and overexpressed CD47, rendering them immune privileged and capable of evading immune rejection in MHC-mismatched allogeneic recipients without the

need for immunosuppression. Another approach involves producing an HLA-matched iPSC line, which requires a significant effort to generate a tissue bank with a sufficient number of selected homozygous HLA-type healthy donors. While these strategies hold promise, several safety concerns need to be addressed before moving human PSC-derived products from the laboratory to clinical settings. These include the potential tumorigenicity of iPSC lines, ensuring the purity and homogeneity of cell products, addressing genetic variations, and resolving any aberrant epigenetic disease-causing memory in the grafts [9].

DRUGS IN PRECLINICAL STAGE FOR PARKINSON DISEASE

Another strategy to mitigate Parkinson's disease (PD) pathology and slow down its progression involves employing medications that target α-synuclein pathology or address other processes associated with PD. Drug repurposing, which involves using existing drugs for new therapeutic purposes, has garnered significant attention in this regard. This approach could accelerate the transition to clinical application since safety and pharmacokinetic data may already exist for these drugs. Below, we examine some of the most notable candidates currently under consideration for PD treatment. One category of drugs that is currently being considered but has not yet entered clinical trials is the β-adrenergic receptor agonists. Recent epidemiological studies and laboratory research have indicated a potential link between these agents, which are commonly used to treat reversible airway obstruction, and a decrease in α-synuclein levels, thus lowering the risk of developing Parkinson's disease. This effect is believed to occur via the modulation of SNCA transcription. Among the drugs that have progressed to clinical trials, exenatide, a glucagon-like peptide-1 (GLP-1) analogue primarily used in the treatment of type two diabetes mellitus, has made significant strides. This compound was trialed in Parkinson's disease patients following promising results with a similar compound, exendin-4, which demonstrated neuroprotective effects in cell and animal models of nigral degeneration. Various mechanisms have been proposed to explain the neuroprotective effects of exenatide through GLP-1 receptor activation, including apoptosis inhibition, reduced microglial activation and neuro-inflammation, decreased oxidative stress, and promotion of neurogenesis. In an initial open-label trial, exenatide was found to be safe in Parkinson's disease patients, although some individuals experienced weight loss.

Furthermore, there was an observed improvement in cognitive and motor function, which persisted even after the cessation of treatment. A subsequent double-blind randomized placebo-controlled trial reported that weekly administration of exenatide was linked to a

reduction in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores compared to the placebo group. Currently, a multicenter phase III trial is in the setup phase, where participants will receive weekly exenatide or placebo (NCT04232969). Additionally, a pegylated form of exenatide known as NLY01, with enhanced pharmacokinetic properties, has entered phase I trials in healthy volunteers, with results pending (NCT03672604).Another drug repurposed for Parkinson's disease is nilotinib, an ABL tyrosine kinase inhibitor primarily used to treat chronic myelogenous leukemia. Nilotinib is thought to enhance autophagy activity by inhibiting ABL, which is crucial for mitophagy initiation, potentially reducing the accumulation of α-synuclein aggregates. An initial phase I trial reported that the drug was well tolerated and safe, with preliminary reports suggesting benefits on motor and cognitive function. However, due to the absence of a placebo group in this study and baseline differences between groups, the clinical effects observed need further investigation. Nevertheless, nilotinib has progressed to randomized placebo-controlled trials (NCT03205488 and NCT02954978), showing a reduction in the ratio of pathogenic oligomeric α-synuclein to total synuclein in cerebrospinal fluid (CSF). However, a recent press release for the NILO-PD trial indicated that while nilotinib was safe and tolerable, it did not offer any clinical benefit. Terazosin, a α1-adrenergic antagonist primarily used in benign prostatic hypertrophy, has emerged as a potential treatment for Parkinson's disease. Terazosin has been found to activate phosphoglycerate kinase-1 and the chaperone protein HSP90, which play roles in various intracellular stress responses. It has demonstrated neuro-protective effects in neurotoxin models of nigrostriatal degeneration and reduced α-synuclein levels in transgenic mice and neurons derived from patients with LRRK2 mutation-associated PD.

Encouraging findings have led to terazosin progressing rapidly to a randomized placebo-controlled trial involving 20 patients with Hoehn and Yahr stage 3 PD (NCT03905811). However, terazosin's ability to reduce blood pressure and induce orthostatic hypotension may limit its applicability in this disease, particularly in patients with advancing PD Apart from targeting α-synuclein clearance pathways, drugs that affect other intracellular pathways may be beneficial in Parkinson's disease. For example, ursodeoxycholic acid (UCDA), a drug used to treat primary biliary cirrhosis, has been found to restore mitochondrial function in cells derived from patients with PARKIN and LRRK2. UCDA has progressed to a randomized placebo-controlled phase II trial, currently recruiting 30 patients with early PD (NCT03840005). Several other agents are either in ongoing or recently completed clinical

trials, as summarized below. Advancements in understanding the pathogenic subtypes of Parkinson's disease (PD) may enable the targeting of specific disease mechanisms in distinct patient groups. One such subgroup comprises patients with GBA1 mutations, present in around 5% of so-called sporadic PD cases. The GBA1 gene encodes glucocerebrosidase, a lysosome enzyme whose activity is diminished in PD patients without GBA1 mutations, making it a promising therapeutic focus for a broader PD population. These mutations are linked to lysosome-autophagy system dysfunction, crucial for α-syncline clearance. Certain GBA1 mutations result in glucocerebrosidase misfolding, hindering its transport to the lysosome and disrupting α-syncline processing. Ambroxol, traditionally an expectorant, has recently undergone trials in patients with GBA1 mutation-associated PD. It has been shown to facilitate glucocerebrosidase refolding and enhance its activity in human cells and transgenic mice, leading to decreased α-syncline levels. The findings from the initial open-label clinical trial of ambroxol in PD patients, with and without GBA1 mutations (Aim-PD), have been recently published. The drug was well tolerated over six months, and there was an associated increase in cerebrospinal fluid (CSF) glucocerebrosidase levels. Alternatively, the glucocerebrosidase pathway can be targeted through glucosylceramide synthase inhibitors, which decrease the levels of glucosylceramide and glucosyl sphingosine, substrates of glucocerebrosidase. While these substrate reduction therapies have been utilized in gauche disease (caused by biallelic mutations in the GBA1 gene), their role in PD pathogenesis is debated. A phase II clinical trial of a glucosylceramide synthase inhibitor (venglustat) in PD patients with GBA1 variants is currently ongoing (MOVES-PD, NCT02906020). Repurposed medications such as nilotinib, inosine, isradipine, iron chelators, and anti-inflammatory drugs are undergoing preclinical evaluation for Parkinson's disease, offering encouraging prospects for future treatment options. Amino chrome represents a viable preclinical model for the advancement of new medications aimed at halting the progression of Parkinson's disease. These drugs target pathways associated with dopamine oxidation, mitochondrial dysfunction, and neuro-inflammation [10].

Table 2. Clinical trials of putative disease-modifying treatments for Parkinson's disease

Drug/class	Proposed mechanism	Progress in trials
-synuclein reduction		
Nilotinib	"Suppression of ABL tyrosine kinase function leading to increased autophagy."	The phase II trial showed the treatment to be well-tolerated but did not demonstrate any clinical advantages.
Terazosin	"Stimulation of PGK1 and HSP90, resulting in elevated ATP levels and decreased levels of α-synuclein."	A randomized, placebo-controlled trial conducted at a single center is currently recruiting participants.
Mitochondrial function		
Ursodeoxycholic acid	Revival of mitochondrial functionality	A placebo-controlled trial with random assignment is currently in the process of enrolling participants.
N-acetylcysteine	The antioxidant impact and increase in glutathione levels.	A phase II study with an open-label design revealed no alterations in markers of oxidative damage or levels of brain glutathione.
Glutathione	Decrease in levels of reactive oxygen species and free radicals	A double-blind trial has concluded without showing any clinical advantages compared to the placebo.
Neuro-inflammation		
Azathioprine	Adjustment of the profile of the peripheral immune system	A placebo-controlled trial, set to commence soon, will be conducted at a single center and is preparing to recruit patients.
Sargramostim (G-CSF)	Stimulation of regulatory T cell (Treg) immune responses	The Phase I trial, which included a placebo group, has concluded. It was generally well-received, with participants experiencing modest enhancements in UPDRS part III scores.
AZD3241	Decreased oxidative stress and neuroinflammation by inhibiting myeloperoxidase.	Phase 2a trial, featuring randomization and placebo control, has concluded. The treatment was deemed safe and well-received, showing a decrease in microglial distribution within the nigrostriatal region.
Other		
Inosine	Increase in urate levels	A phase III trial, randomized and placebo-controlled, was stopped prematurely in 2018, and the results are pending.
Exenatide	Activation of GLP-1 receptors results in the prevention of apoptosis, decreased activation of microglia, and reduced neuroinflammation, oxidative stress, along with the promotion of neurogenesis.	The treatment was well-received, and improvements were observed in UPDRS part III scores in a randomized controlled trial. Currently, preparations are underway for a Phase III trial.
Isradipine	Protection of neurons via the inhibition of L-type calcium channels in the substantia nigra.	A Phase III trial conducted across multiple centers has recently concluded, showing no enhancements in motor function or quality of life outcomes.
Deferiprone	Chelation of iron	A Phase II trial, utilizing randomization and a double-blind, placebo-controlled design, has been finished, revealing a decrease in iron levels in the caudate and dentate nucleus. However, no notable clinical advantages were observed.

GLOBAL SCENARIO OF PARKINSON DISEASE

The International Classification of Diseases ninth revision (ICD-9) codes utilized in the analysis of Parkinson's disease-related mortality are 332 (Parkinson's disease), 332.0 (paralysis agitans), and 332.1 (secondary Parkinsonism), while the corresponding ICD-10 codes are G20 (Parkinson's disease), G21 (secondary Parkinsonism), and G22 (Parkinsonism in diseases classified elsewhere). A common case definition for Parkinson's disease employed in many epidemiological studies involves the presence of at least two of the four primary symptoms: rest tremor, bradykinesia, stiffness of the limbs and torso, and postural instability. Alternative definitions, such as the UK Parkinson's Disease Society Brain Bank criteria, along with a doctor's diagnosis of Parkinson's disease and the prescription of Parkinson's disease-specific medications, were also considered. Additionally, we included three years of medical claims data (years 2000, 2010, and 2012) from the USA. For diseases like Parkinson's disease, it was anticipated that the data from claims sources would align with the true prevalence, assuming that most patients would seek medical attention each year. In cases where data points from epidemiological studies covered age spans of more than 20 years, we segmented the data points using the age distribution observed in the USA, which provided the most detailed age data available. For Parkinson’s disease, significant disparities have been observed between mortality data and non-fatal data. For instance, US vital registration data indicate a more than threefold increase in age-standardized death rates attributed to Parkinson’s disease since 1980, without a corresponding rise in prevalence data over the same period. Additionally, substantial variation—exceeding 25 times—exists across different countries in age-standardized mortality rates for the most recent year of available vital registration data. However, such heterogeneity is not observed in non-fatal data. These differences likely stem from changes and inconsistencies in coding practices for certifying deaths attributed to Parkinson’s disease. To address this bias, we adopted a joint modeling approach for both prevalence and mortality from Parkinson’s disease. Initially, we employed CODEm for cause of death modeling and DisMod-MR 2.1 for non-fatal modeling. The CODEm model utilized 14,990 site-years of data, incorporating predictive covariates such as SDI, cumulative cigarette consumption, healthcare access and quality, education, and mean cholesterol level.

In the DisMod-MR 2.1 model, we assumed no remission (i.e., no cure) and no incidence before the age of 20 due to the rarity of the disease before this age. We excluded incidence data due to inconsistencies with available prevalence data and adjusted medical claims data to

rectify systematic under-reporting. Next, we identified countries with high-quality vital registration systems, age-standardized prevalence exceeding five per 10,000, and a population exceeding one million. Among these, Austria, Finland, and the USA exhibited the highest ratios of cause-specific mortality to prevalence. We used the log-transformed ratios from these countries to conduct a fixed-effects regression with dummy variables on age and sex. This regression provided excess mortality data, representing the excess rate of death among individuals with Parkinson's disease compared to the general population. Subsequently, we incorporated the excess mortality data into a second DisMod-MR 2.1 model, maintaining consistency with the initial model in terms of settings and covariates.

The cause-specific mortality and prevalence results obtained from this model were considered final outputs, ensuring coherence between non-fatal input data and excess mortality rates from the three countries most likely to code Parkinson's disease as a cause of death. To the Hoehn and Yahr stages. We drew from 30 distinct sources, covering nine of the 21 world regions, and categorized a Hoehn and Yahr score of 2.0 or lower as mild Parkinson's disease, 2.5–3.0 as moderate Parkinson's disease, and 4.0–5.0 as severe Parkinson's disease. These findings were used in meta-analyses to determine the proportions of Parkinson's disease cases classified as mild, moderate, and severe. Subsequently, we applied these proportions to split the overall prevalence of Parkinson's disease into the respective severity categories. Finally, we multiplied the prevalence of each severity category by disability weights specific to each severity level to compute YLDs. To account for comorbidity, we employed a simulation method that attributed all non-fatal outcomes to hypothetical individuals and adjusted disability in patients with multiple conditions [11]. From 1994 to 2019, there has been a notable increase in Parkinson's disease mortality worldwide, particularly among older individuals and men. This underscores the importance of tailored healthcare planning and delivery to address this trend. Between 1990 and 2016, the global impact of Parkinson's disease has more than doubled, marked by rising prevalence rates. In 2016 alone, it led to 3.2 million disability-adjusted life years (DALYs) and 211,296 deaths. Parkinson's disease is associated with worldwide changes in brain structural connectivity, such as reduced clustering coefficient and global efficiency, as well as increased characteristic path length, reflecting disturbances in network organization. Parkinson's disease is experiencing a rapid global rise, with notable discrepancies in healthcare access and medication availability, particularly in low- and middle-income nations, demanding immediate attention.

CONCLUSION

As our capacity to generate authentic midbrain dopaminergic neurons from stem cell sources advances, the prospect of conducting a pioneering clinical trial in Parkinson's disease patients becomes increasingly tangible. Well-established protocols for deriving dopamine precursor cells are yielding a substantial number of cells with clinical relevance. While this review has underscored the benefits and prospects of stem cell therapy, numerous questions and barriers persist.

Presently, the primary hurdles impeding the clinical application of stem cells revolve around ethical considerations, tumorigenesis, immune responses, and, to some extent, toxicity. Significant ethical concerns surround the use of human embryonic stem cells (hESCs), which provoke robust immune reactions. In contrast, induced pluripotent stem cells (iPSCs) pose fewer ethical dilemmas and exhibit reduced immune rejection. However, their potent pluripotency raises concerns regarding tumor formation, particularly when derived from Parkinson's disease patients who may harbor pathological gene mutations affecting the outlook for cell replacement therapy. As induced pluripotent stem cell (iPSC) technology has advanced, cell transplantation emerges as a promising and reliable therapy. Transplanted cells in non-human primates exhibit prolonged survival and functionality exceeding 2 years post-transplantation, without any indications of tumor formation, underscoring the safety and efficacy of this approach. Nonetheless, the necessity for immunosuppressive medications persists due to the absence of "universal stem cells" that evade immune rejection. The outcomes of ongoing and forthcoming trials conducted by the global consortium G Force-PD are eagerly anticipated, as their success could pave the way for the widespread application of cell therapy in treating Parkinson's disease and other degenerative conditions. In summary, while we are not yet exploring disease-modifying treatments, stem cell. Transplantation holds promise as a potential forefront therapy for Parkinson's disease in the future.

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