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REVIEW

Unravelling the Parkinson's puzzle, from medications and surgery to stem cells and genes: a comprehensive review of current and future management strategies

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder, prevalent in the elderly population. Neuropathological hallmarks of PD include loss of dopaminergic cells in the nigro-striatal pathway and deposition of alpha-synuclein protein in the neurons and synaptic terminals, which lead to a complex presentation of motor and non-motor symptoms. This review focuses on various aspects of PD, from clinical diagnosis to currently accepted treatment options, such as pharmacological management through dopamine replacement and surgical techniques such as deep brain stimulation (DBS). The review discusses in detail the potential of emerging stem cell-based therapies and gene therapies to be adopted as a cure, in contrast to the present symptomatic treatment in PD. The potential sources of stem cells for autologous and allogeneic stem cell therapy have been discussed, along with the progress evaluation of pre-clinical and clinical trials. Even though recent techniques hold great potential to improve the lives of PD patients, we present the importance of addressing the safety, efficacy, ethical, cost, and regulatory concerns before scaling them to clinical use.

Keywords Parkinson's disease · Deep brain stimulation · Stem cell therapy · Gene therapy

Parkinson's disease (PD)

Parkinson's disease (PD) was first medically described in 1817 when James Parkinson published "An Essay on the Shaking Palsy" (Parkinson 1969, 2002). Later, various neurologists and pathologists described the significant clinical and pathological features of PD, separating PD from other neurological conditions (Goetz 2011). PD is a progressive neurodegenerative disorder pathologically characterised by neuronal inclusions in the form of Lewy bodies and Lewy neurites composed mainly of misfolded alpha-synuclein (α-synuclein) species. It is therefore classified as a Lewy-type synucleinopathy (Tolosa et al. 2021). The degeneration and loss of dopaminergic (DA) neurons in the substantia nigra (SN) and the projections from the substantia nigra pars compacta (SNc) to the striatum are responsible for the cardinal motor symptoms such as tremor, bradykinesia, and rigidity. PD has florid non-motor manifestations such as anxiety, depression, sleep dysfunction, dysautonomia, and a variety of neuropsychiatric and cognitive changes (Hayes 2019). These symptoms result from widespread neurodegeneration happening both in dopaminergic projections to the non-motor circuits of the basal ganglia and the non-dopaminergic neurons in the brain, such as the brainstem serotoninergic, adrenergic, and cholinergic systems. The deposition of Lewy bodies happens in neurons, presynaptic terminals, and glia. These deposits also accumulate in other parts of the body

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outside the brain, such as the olfactory bulb, the retina, the sympathetic and parasympathetic ganglia, and the skin.

Affecting nearly 8–11 million people worldwide, Parkinson's disease is the second most common neurodegenerative disorder next to Alzheimer's disease. PD is considered a late-onset disorder with increased prevalence with age. The mean age of onset of PD is approximately 60 years. However, around 10% of cases have their onset before 50 (early-onset PD), even in their teens or 20 s, and rare juvenile onset has also been also observed (Pagano et al. 2016; Bhat et al. 2018). PD affects about 0.3% of the general population in industrialised countries; the prevalence in the elderly above 60 years is around 1%. Age-related prevalence increases both for men and women (Sveinbjornsdottir 2016). The likelihood of developing PD depends on genetic variations in certain genes, environmental factors, and lifestyle. Genetic factors play a critical role in those with younger age of onset. Mutations in the genes LRRK2, SNCA, and VPS35 can cause dominantly inherited PD with varying levels of penetrance and PRKN, PINK1, and PARK7 genes in recessively inherited PD (Nuytemans et al. 2010). On top of these genes responsible for familial PD with a Mendelian pattern of inheritance, several susceptibility loci and other genes increasing the risk of PD have been identified in genome-wide association (GWA) studies (Bandres-Ciga et al. 2020). Polymorphisms in GBA, the gene encoding the lysosomal enzyme glucocerebrosidase (GCase) and implicated in the lysosomal storage disorder, Gaucher's disease, is also known to contribute to increased risk of PD (Zheng and Fan 2022). Many of the so-called idiopathic forms of PD also have a genetic background, as many cases result from the synergistic action of genetic factors, increasing the risks and environmental factors such as pesticides or infections (Kline et al. 2021). The treatment for PD includes medications and functional neurosurgery in selected cases. Currently, available treatment options only manage the symptoms and improve patients' quality of life but do not provide a cure, reverse the neuropathological changes like loss of dopaminergic (DA) neurons, or even slow down the progression of the disease.

Pathological hallmarks of PD

Even though the cause for the progressive neurodegeneration in PD is unknown, the underlying pathological characteristics causing motor as well as non-motor symptoms are as follows.

Lewy body deposition in the brain

The cellular buildup of Lewy bodies and Lewy neurites in the substantia nigra and other areas is an important pathogenic aspect of PD. Lewy bodies are rounded eosinophilic inclusions that are present inside the neurons in PD. They comprise more than 90 proteins; the significant components are α-synuclein and ubiquitin (Balestrino and Schapira 2020). The major component of Lewy bodies and neurites is aggregated α-synuclein, which has undergone several post-translational changes such as phosphorylation, ubiquitination, nitration, and oxidation of certain residues (Braak et al. 2003a). The aggregated α-synuclein disrupts the microtubule-based subcellular transport, which may lead to synaptic dysfunction and disruption of neuronal homeostasis (Singleton et al. 2013). The deposition of Lewy bodies in PD subjects has been identified in the neurons in the medulla oblongata, pons, and the olfactory bulb during the early stages. This is followed by the spreading of Lewy body pathology to the midbrain where the SN is located, and eventually into the neocortex as the disease progresses (Braak et al. 2003a).

Neurodegeneration of DA neurons in the nigrostriatal system

Parkinson's disease is distinguished by the loss of DA neurons of the substantia nigra region of the midbrain and their principal axon projections to the striatum (Lotharius and Brundin 2002). The death of DA neurons in the nigrostriatal system is critical in the pathophysiology of motor and some non-motor symptoms of PD as illustrated in Fig. 1. The pathological changes underlying PD start many years before the appearance of the initial symptoms; nearly 70–80% of the DA axon terminals in the striatum had already degenerated by the time the first motor symptoms appear (Kolacheva et al. 2023).

Dysfunction of multiple neurotransmitter systems

Extranigral sites, including the locus coeruleus and subcoeruleus complex, reticular formation and raphe nuclei, dorsal nuclei of the vagus, and nucleus basalis of Meynert also exhibit cell loss (Del Tredici et al. 2002). Motor impairment in PD is attributed primarily to the degeneration of DA nigrostriatal neurons with the appearance of intraneuronal Lewy bodies; however, similar damage may occur to the cytoskeleton of glutamatergic, cholinergic, GABA-ergic, tryptaminergic, noradrenergic, and adrenergic nerve cells also (Sveinbjornsdottir 2016).

Oxidative stress and inflammation

Oxidative stress and neuroinflammation are the key factors thought to contribute together to the development of PD (Taylor et al. 2013). Reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and hydroxyl free radicals can harm neurons if they are created in excess, as happens during persistent neuroinflammatory responses. The

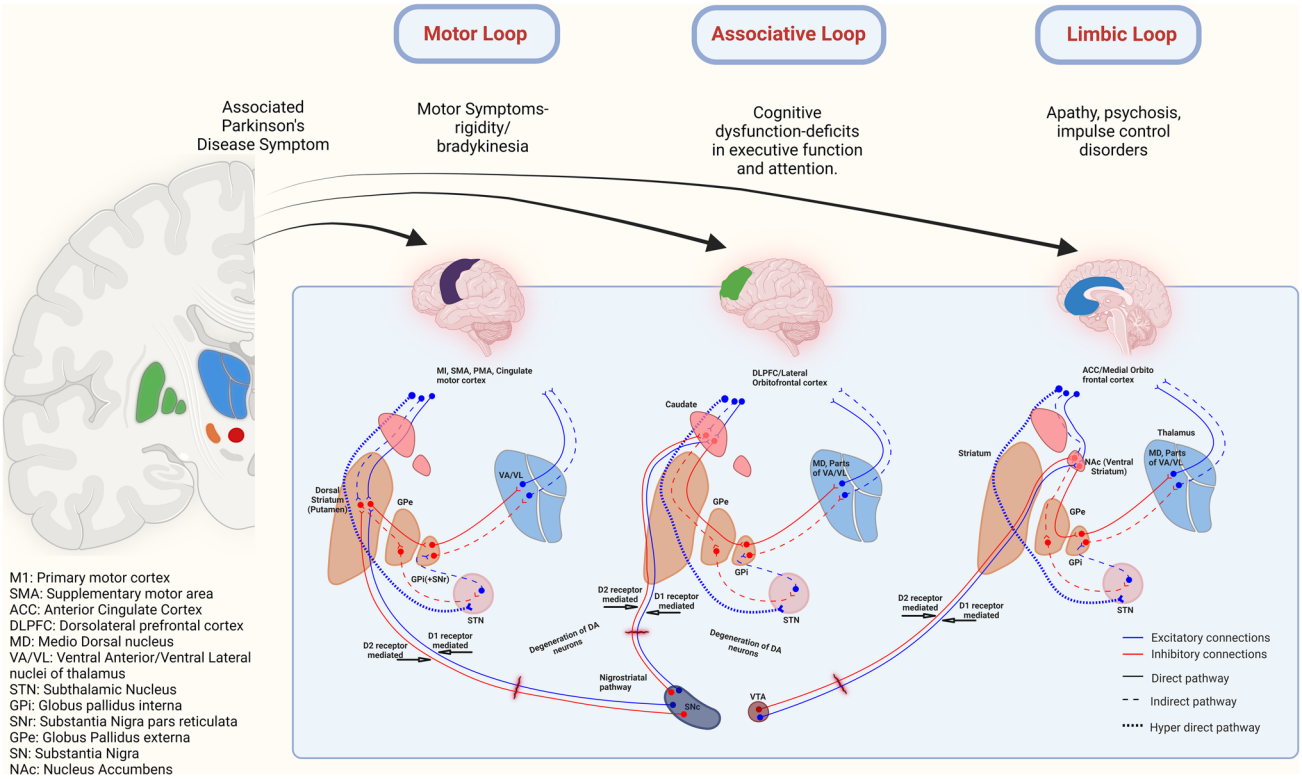

Fig. 1 The motor, associative, and limbic basal ganglia circuits. The degeneration of DA neurons in the nigrostriatal pathway in Parkinson's disease patients causes associated symptoms. The degeneration of DA neurons from the substantia nigra pars compacta to the dorsal striatum (putamen) causes motor symptoms of rigidity and bradykinesia. Similar degeneration of the nigrostriatal tracts from SNc to caudate results in cognitive changes such as executive changes and attention deficits. The limbic loop involves dopaminergic projections from the VTA to the ventral striatal regions of the nucleus accumbens whose degeneration contributes to the pathogenesis of apathy, psychosis, and impulse control disorders (image generated in Biorender)

nitrogen intermediates, nitric oxide, and peroxynitrite also cause oxidative damage to the neurons (Mosley et al. 2006).

Synuclein aggregation and neuronal death are accompanied by a neuroinflammatory reaction that is driven by the glia. Glial cells are essential components of homeostatic systems that support neuronal survival in the brain's niche (Tansey and Goldberg 2010). Free radicals such as NADPH and iNOS, produced by microglia, are a key link between neuroinflammation and synuclein dysfunction in driving chronic PD neurodegeneration. It is reported that inhibition of NADPH oxidase and iNOS reduce pathologic alterations of α-synuclein which causes chronic neurodegeneration in PD (Gao et al. 2011)

Mitochondrial and autophagy dysfunction

Mitochondrial dysfunction in PD is characterised by the reduction of mitochondrial complex I enzyme activity, leading to the generation of oxidative stress in the nigral neurons and their accelerated degeneration. DA neuronal death is also associated with misfolding and aberrant degradation of brain proteins. The presence of misfolded and ubiquitinated proteins shows that dysregulation of protein synthesis or flaws in the protein breakdown pathway play a significant role in PD etiology (Vila and Przedborski 2004). Dysfunction of autophagy or lysosomal degradation pathway is found to be associated with impaired protein or organelle clearance. It can contribute to intracellular protein aggregates, which leads to the eventual death of neurons in the PD brain. (Rivero-Ríos et al. 2016).

Supplementing dopaminergic activity in the nigrostriatal pathway is the principle behind most medical treatment options for the motor symptoms of Parkinson's disease. Deep brain stimulation (DBS), the invasive treatment widely used in the management of advanced stages of PD, does not increase nigrostriatal dopaminergic activity, but attempts to correct the neuronal circuit dysfunction resulting from DA deficiency by electrically stimulating nuclei like the subthalamic nucleus (STN) or Globus Pallidus. Current researches focus on repairing the nigrostriatal pathway to restore dopamine levels in the striatum (Harris et al. 2020). Since endogenous DA neuronal cells are insufficient or defective in PD, DA cell delivery could restore the nigrostriatal circuit.

Current diagnosis and management of PD

PD is a multifaceted neurodegenerative disorder with motor and non-motor symptoms manifesting differently in each patient (Jankovic 2008; Thenganatt and Jankovic 2014). PD-like symptoms are seen in certain other neurological disorders such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), collectively known as "atypical parkinsonian disorders". The etiology, neuropathology, and disease progression of these conditions are different from those of PD. However, the clinical syndrome of parkinsonism (presence of bradykinesia with rigidity and/or tremor) is shared by PD and these disorders. A meticulous clinical assessment is needed to differentiate such disorders from PD.

Diagnosis of PD

The gold standard for diagnostic confirmation of PD is post-mortem examination and demonstration of cell loss in the SN region with the presence of Lewy bodies, staining positive for α-synuclein and ubiquitin (Hartmann 2004). In a clinical setting, the diagnosis of PD can be made with a certainty of 75–90% based on medical history and clinical examination. Several clinical diagnostic criteria have been in use for PD. The UK Parkinson's Disease Society Brain Bank (UKPDSBB) criteria (Hughes et al. 1992) have been the most widely used. The International Parkinson and Movement Disorders Society (MDS) has recently proposed more elaborate criteria (MDS Diagnostic Criteria) for the diagnosis of PD (Postuma et al. 2015). All the currently used diagnostic criteria rely on identifying the core motor symptom complex of parkinsonism and then looking for additional features supportive of a diagnosis of PD and ensuring the absence of features ("red flags") suggestive of other parkinsonian disorders like MSA and PSP

Clinical symptoms

Motor symptoms Motor symptoms in PD are generally distributed asymmetrically (one side of the body is generally affected initially and continues to be the more severely affected side). Symmetrical symptoms, though they could occur in PD, should raise the suspicion of atypical parkinsonian disorders such as MSA or PSP. Parkinsonism is the core motor symptom of PD. Parkinsonism is a clinical symptom complex characterised by bradykinesia with rigidity and/or tremor. Postural instability is a common accompaniment of parkinsonism, particularly in the later stages of PD.

(a) Bradykinesia: Bradykinesia means slowness of movements, though muscles can exert normal power. Initiation and execution of voluntary movements, including limb movements, gait, and facial expression, become slow (Berardelli et al. 2001).
(b) Tremor: The classical tremor in PD is characterised by a 4-6 Hz resting tremor, which is generally unilateral or asymmetrical. Action and postural tremors also could occur in PD (Anouti and Koller 1995). When the tremor occurs in the hands, it is often described as a "pill-rolling" tremor because of the characteristic pattern.
(c) Rigidity: Muscle rigidity in PD is characterised by wax-like resistance during passive movement of the limbs. This, combined with tremors, often results in a "cogwheel" feeling during examination (di Biase et al. 2018).
(d) Postural instability: Postural instability is generally a late feature of PD and is characterised by the loss of automatic balance control resulting in a tendency to fall (Palakurthi and Burugupally 2019).

Based on the dominant symptoms, different PD phenotypes can be identified (Foltynie et al. 2002). These include tremor dominant (TD), postural instability and gait dominant (PIGD), and mixed/indeterminate types (Marras and Lang 2013). TD PD is likely to progress slowly and have a relatively benign course compared to the PIGD variant.

Non-motor symptoms Parallel to this, many non-motor symptoms precede the motor symptoms and then progress through the later stages of PD.

(a) *Olfactory dysfunction* Lack of odor discrimination is presented in 70–90% of PD patients in the early stages and can precede the development of motor symptoms (Doty 2012).
(b) *Dysautonomia* Autonomic failure in PD includes orthostatic hypotension, constipation, gastrointestinal dysfunction, urinary incontinence, and sexual dysfunction which can occur at the early stages and worsen in the later stages of the disease (Goldstein 2014).
(c) *Depression and anxiety* These are observed in roughly 40% of the patients, along with motor symptoms, and may correlate with disease severity. These symptoms contribute to significant functional impairment and poor quality of life (Ray and Agarwal 2020).
(d) *Cognitive decline and dementia* Mild cognitive dysfunction, not qualifying for the diagnosis of dementia, can be present even in the early stages of PD. Cognitive dysfunction and dementia progress during PD and, in 15–20 years, become ubiquitous (Hely et al. 2008; McKeith et al. 2017).

(e) *Rapid eye movement (REM)-sleep behaviour disorder (RBD)* RBD or dream enactment can occur years before the onset of motor symptoms of PD. This is characterised by vigorous limb movements and vocalisation resulting from complex motor enactment of dreams (Tekriwal et al. 2017).

Imaging in PD diagnosis

Conventional magnetic resonance (MR) imaging sequences used in routine clinical practice are generally normal in PD. MR imaging may help in differentiating PD from atypical parkinsonian disorders such as MSA and PSP in some cases. Higher-field MR imaging studies make use of high-resolution susceptibility-weighted imaging (SWI) to detect neurodegeneration in the substantia nigra pars compacta (SNpc) present in PD patients through the absence of dorsal nigral hyperintensity (DNH), which appears in the shape of a "swallowtail" in healthy individuals (Pavese and Tai 2018). The "loss of swallowtail sign" in PD results from changes in iron deposition in the nigrosome-1 region.

Neuromelanin MR imaging (NM-MRI) is sensitive to neuromelanin, a dark intracellular pigment found in SNc and locus coeruleus (LC). It is susceptible to oxidative stress(Zecca et al. 2008). The study on the utility of NM-MRI for differential diagnosis of PD and atypical parkinsonian disorders (APDs) has gained attention in the last decade, but is yet to be accepted clinically (Ohtsuka et al. 2014; Taniguchi et al. 2018). Pre-synaptic dopaminergic imaging using PET and SPECT tracers differentiates degenerative parkinsonism from non-degenerative conditions. Dopamine transporter (DAT)-SPECT imaging is FDA approved for the differentiation of tremulous forms of parkinsonism from essential tremor (ET); it is typically abnormal in PD and other neurodegenerative parkinsonism disorders while normal in ET. Normal functional neuroimaging of the presynaptic dopaminergic system is considered an absolute exclusion criterion for the diagnosis of PD in the MDS criteria for clinical diagnosis of PD (Postuma et al. 2015).

Genetic testing

Genetic testing is currently available for clinical use, particularly in young-onset PD (YOPD) patients. In the absence of gene-specific treatments at present, genetic test results are used primarily for counselling and prognostication. Moreover, certain genetic forms of PD, e.g. PD associated with pathogenic variants in the gene for glucocerebrosidase (GBA), may respond differently to interventions like DBS compared to those without such variants (Pal et al. 2022). Genetic testing may become more critical in the future when gene-specific therapies emerge (Axelsen and Woldbye 2018).

An important factor supporting the diagnosis of PD is the response to dopaminergic therapy; a poor response to dopaminergic medications like levodopa tried at a sufficient dose is a factor pointing strongly to a diagnosis of a parkinsonian disorder other than PD (Lingor et al. 2011). The conditions to be suspected in such cases include other neurodegenerative pParkinsonisms, such as PSP, MSA, and corticobasal degeneration (CBD), and secondary ("non-degenerative") parkinsonian disorders like vascular parkinsonism, normal pressure hydrocephalus (NPH), and drug-induced parkinsonism. The efficient management of parkinsonian disorders relies on their proper diagnosis.

Management of PD

The management options for PD have to be tailored to the needs of the individual patients based on the profile of symptoms, level of impairment, age, and co-morbid status. At present, there are no proven neuroprotective medications that can cure PD or modify its disease course; therefore, medical and surgical management is purely oriented towards control of symptoms and improving quality of life. Supportive measures such as physiotherapy to ease movements and improve balance, occupational therapy to maintain independence, speech therapy to maintain communication skills, and dietary advice to alleviate symptoms like constipation, and to maintain optimal weight, are also recommended to improve the quality of life. In this section, we briefly discuss some of the current medications and surgical options for PD.

Medications

Dopamine replacement therapies form the mainstay of the medical management of PD (Borovac 2016). The medications are prescribed based on the symptoms, disease duration, and age of the patient and are aimed at controlling symptoms that cause disability and handicap. The medications used in the treatment of PD are briefly described below:

(a) *Levodopa* Since the motor symptoms of PD stem from the degeneration of dopaminergic neurons projecting to the striatum and resultant dopamine deficiency in the striatum, the most effective medication is levodopa, which is the precursor to dopamine (Poewe et al. 2010). It enters the bloodstream and crosses the blood–brain barrier and gets decarboxylated to dopamine in the remaining dopaminergic terminals in the striatum, thus reducing the symptoms of PD. To reduce the breakdown of L-Dopa in the bloodstream before reaching the brain and to reduce the side effects resulting from decarboxylation happening in the periphery, it is usually combined with benserazide or carbidopa (Gold-

stein et al. 1984). Long-term use of levodopa has been associated with levodopa-associated complications such as uncontrollable involuntary movements called levodopa-induced dyskinesia (LID) and other motor complications resulting in "on–off" effects (Marsden and Parkes 1977; Marsden 1994). To reduce the risk of dyskinesia, levodopa treatment is generally postponed, particularly in younger patients, managing with other drugs like dopamine agonists till levodopa treatment becomes unavoidable because of the increasing severity of parkinsonism, and started and maintained at a lower dose as far as possible. However, this approach has also been challenged; levodopa should not be withheld even in young patients in whom initiation of levodopa is judged to be essential for providing improvement in quality of life (Vijayakumar and Jankovic 2016).

(b) *Dopamine agonists* Dopamine agonist medications like pramipexole and ropinirole are used as a substitute for dopamine and have a milder effect than levodopa. They directly act on the DA receptors without increasing presynaptic dopamine synthesis in the striatum. They are given more frequently compared to levodopa in the early stages of PD and in younger patients; they are also prescribed in combination with levodopa to augment the action of levodopa and keep the levodopa dose low. Thus, by helping to reduce the dose of levodopa, the onset of LID can be delayed. They have similar, but more severe adverse effects than levodopa and can cause abdominal discomfort, nausea, hallucinations, confusion, and increased sleepiness (Borovac 2016). Dopamine agonists are generally poorly tolerated by elderly patients. They have also been associated with compulsive behaviours such as addictive gambling, shopping, and increased sexual desire.

(c) *MAO-B/COMT inhibitors* Monoamine oxidase isoform B (MAO-B) and catechol-O-methyltransferase (COMT) are both enzymes involved in dopamine metabolism and breakdown. Thus, by inhibiting the activity of these enzymes, the level of dopamine is increased, thereby reducing the symptoms associated with striatal dopamine depletion in PD. MAO-B inhibitors can be prescribed as monotherapy in the early stages of PD or along with other medications like levodopa or dopamine agonists. COMT inhibitors are therapeutically useful only when given along with levodopa.

(d) *Anticholinergics* Anticholinergics do not act through dopamine replacement and could be used for symptomatic treatment in some patients, particularly for tremors. They are generally prescribed with dopamine replacement therapy (Katzenschlager et al. 2002). They block the action of acetylcholine and ameliorate the tremor symptoms in PD. Side effects include dry mouth, blurred vision, hallucinations, and changes in attention and memory. Hence, it may not be safe for elderly patients or those who already have cognitive or neuropsychiatric symptoms (Ehrt et al. 2010).

Symptoms such as dysarthria, dysphagia, and freezing of gait do not respond well to dopaminergic treatment and may need measures like physiotherapy and speech therapy. Timely identification and management of non-motor symptoms are equally as important as managing motor symptoms to ensure good quality of life for patients. The interventions include treatment of constipation by dietary measures and laxatives, appropriate use of antidepressants and anxiolytics for depression and anxiety, and management of sleep disturbances, fatigue, and sexual dysfunction. Patients also need to be carefully monitored for adverse effects of dopaminergic treatment, including hallucinations and behavioural disturbances, impulse control disorders, and compulsive behaviours, and dose adjustments need to be made if these are detected (Weintraub et al. 2010; Martini et al. 2018)

Neuroprotective drugs capable of arresting or slowing down the neurodegenerative process, thereby favorably modifying the course of the disease, remain to be an unmet need in the management of PD (Lang and Espay 2018). Multiple genetic and environmental mechanisms and multiple cellular cascades contribute to the pathogenesis of PD. The heterogeneity of the etiology and patho-mechanisms underlying PD is a major challenge in the successful development of effective neuroprotective drugs. Precision medicine, aimed at individualising management based on the genetic mechanisms in the individual patient, is a novel and emerging strategy (von Linstow et al. 2020). Drug repurposing, or studying the drugs that are already approved to treat one disease for their safety and efficacy in other diseases, is a promising option in the development of neuroprotective agents in PD (Fletcher et al. 2021). Several drugs including antidiabetic drugs, antihypertensives, and some anticancer drugs have undergone repurposing trials in PD. Some of them such as ambroxol (traditionally used as a mucolytic agent) and exenatide (antidiabetic drug) have shown promising results warranting further studies (Athauda et al. 2017).

Deep brain stimulation (DBS) surgery

DBS is a relatively safe surgical procedure in which electrodes (DBS leads) are implanted in the nodes in the subcortical motor network. The electrode contacts at the lead tips are used to stimulate the target nuclei at finely tuned amplitude, frequency and pulse width to provide symptomatic relief in many movement disorders such as PD, dystonia, and ET. It is currently the standard of care for PD patients who develop motor complications—motor fluctuations and LID—which impair quality of life despite optimal

tailoring of medical management (Hartmann et al. 2019). It requires meticulous patient selection based on strict eligibility criteria, which include age, disease duration and severity, response to levodopa treatment, burden of neuropsychiatric dysfunction, and co-morbidity status. A meticulous follow-up by an experienced comprehensive care team is essential for the patients to enjoy the maximum benefits of this surgical treatment (Krishnan et al. 2018). Patients who respond to levodopa treatment usually respond to DBS. The exact mechanism by which it ameliorates the symptoms of movement disorders remains elusive. The widely accepted theory is that the high-frequency stimulation of DBS acts as an "information lesion" disrupting the pathological neuronal hyper-synchrony in the neural circuits passing through the target nuclei, thereby blocking the flow of abnormal information and relieving symptoms (Grill et al. 2004).

The subthalamic nucleus (STN) and globus pallidus internus (GPi) are the common nuclei targeted in DBS for PD. STN, as in Fig. 2, is generally the preferred target to treat motor symptoms and often enables the reduction of medication doses and, thereby, control of LID (Groiss et al. 2009). GPi-DBS has a direct anti-dyskinetic effect compared to STN-DBS, but reducing the medication dose is usually not possible (Fan et al. 2020). The gait and postural symptoms generally remain refractory or show only transient benefits following STN or GPi DBS. Pedunculopontine nucleus (PPN) has been tried as a target in those with predominant gait and postural symptoms, with variable results (Yu et al. 2022).

The implantation of the DBS leads is conventionally done using a stereotactic frame; frameless and robotic DBS are emerging as novel alternatives. The intracranial end of the lead, placed in the target nuclei, has quadripolar or octopolar electrode contacts. The extracranial end of the leads is connected to the pulse generator placed in the infraclavicular pocket of the chest wall using extension wires. To ensure accurate placement of the electrodes and avoid any adverse effects, micro-electrode recording (MER) is performed during the surgical operation while the patient is awake. A couple of days following the surgery, the pulse generator is programmed by adjusting the amplitude, frequency, and pulse width of the neurostimulation. Multiple programming sessions may be required to ensure maximum benefit with minimum side effects to the patient. Repeat programming sessions may also be necessary to deal with symptoms arising from the worsening of the disease over time. Medications are adjusted gradually as the symptoms improve with stimulation; though dose reduction is often possible,

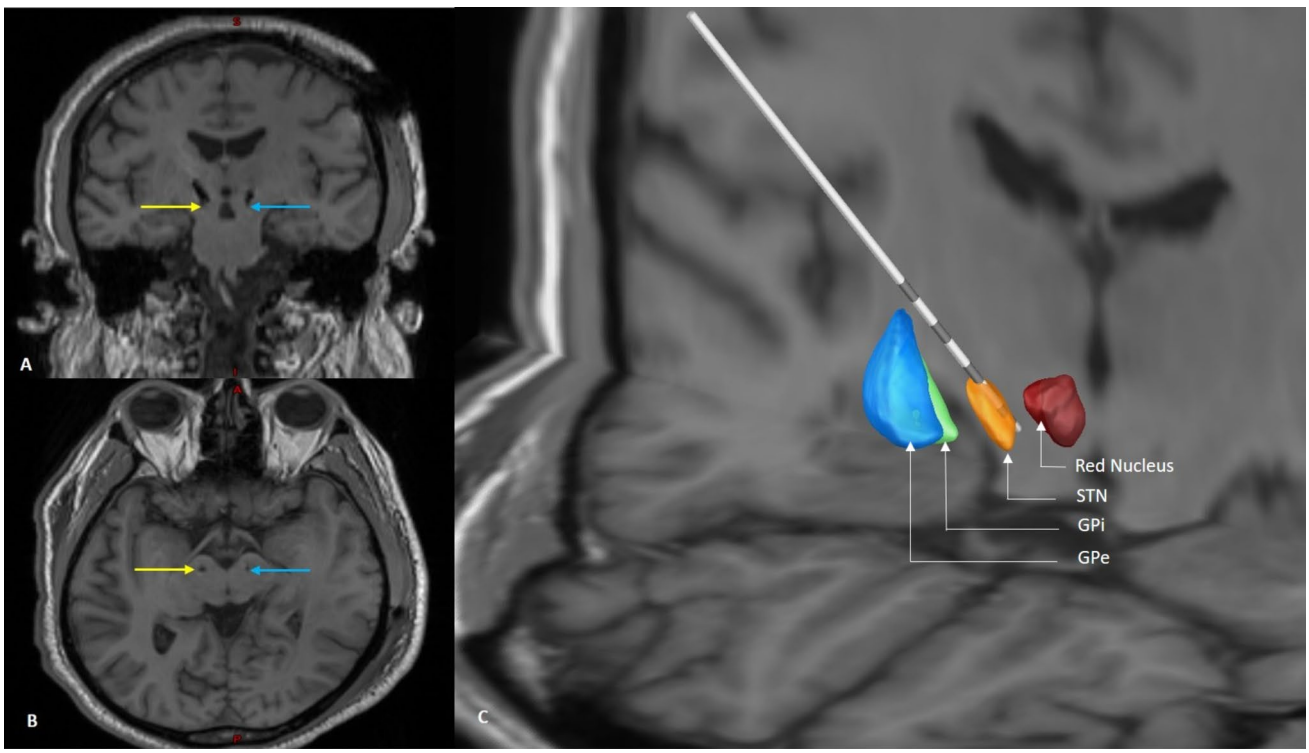

Fig. 2 Figure showing the reconstructed lead placement for STN-DBS surgery performed in one of the patients at the Comprehensive Care Center for Movement Disorders, SCTIMST, Trivandrum. **A** Coronal, **B** axial slice with arrows showing the tips of the DBS lead implanted in the STN in the postoperative MRI. **C** 3-D reconstruction of the lead position from the postoperative MRI with electrode tip located in the STN

particularly following STN DBS, complete withdrawal of medications is not recommended (Fasano et al. 2016). Even though there is no neuroprotective effect, DBS improves symptoms and quality of life for several years (Kishore et al. 2010; Krishnan et al. 2016). Surgical complications include implant infections and intracranial haemorrhage during the surgical procedure. Recent advances in DBS technology include the use of intraoperative imaging, current steering, and directional stimulation using specialised electrodes to maximise benefits (Steigerwald et al. 2019), and adaptive DBS, or closed-loop stimulation, which depends on signals from target nuclei to tailor stimulation parameters optimally (Fleming et al. 2020).

Other device-assisted therapies which can be used in selected patients unsuitable for DBS include levodopa–carbidopa intestinal gel (LCIG—delivery of levodopa continuously and directly into the duodenum) and apomorphine pump. Oral medications, DBS, and other such device-assisted therapies have several limitations. Though these therapies manage symptoms and improve quality of life, they do not have any impact on the disease progression and hence cannot prevent patients from relentlessly progressing to the late-stage of PD, characterised by medication- and stimulation- resistant symptoms like imbalance and falls, dysarthria, dysphagia, and cognitive dysfunction. These warrant research for better treatment alternatives, such as cell-based therapies or gene therapy for restoring the lost neurons and modifying the natural course of the disease.

Stem cell therapy for PD

Cell replacement therapy may compensate for the loss of DA neurons in PD. Restoration of the lost DA neurons has the potential to cure PD rather than merely addressing the symptoms as with current treatments. Transplantation of dopamine-producing neurons or immediate precursors of DA neurons into the PD brain is one of the various cell therapy strategies. DA neurons or immediate precursors of DA neurons may be collected from autologous or allogeneic sources such as foetal tissue and embryonic stem cells (ESC). In autologous cell therapy, the cells are sourced from the patient as adult stem cells or induced pluripotent stem cells (iPSCs) as shown in Fig. 3. In foetal cell therapy, the neural cells are directly collected from the foetal tissue. The DA neurons or progenitors derived from autologous sources are usually genetically manipulated to induce differentiation. The directed differentiation of the stem cells using small molecules or growth factors without viral vectors or genetic methods is another approach.approximately 300 000 cells

The proof of concept or pre-clinical studies for cell-based therapies utilise animal models based on MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and 6-OHDA (6-hydroxydopamine). These chemicals recapitulate PD-like symptoms in rodents and non-human primates to evaluate the potential and safety of cell replacement therapy in PD. The MPTP neurotoxicity and its effects in human brain was discovered in 1982 when seven young adults in California injected themselves with synthetic heroin, which contained MPTP, and developed severe and irreversible parkinsonism (Langston 2017; Nonnekes et al. 2018). Understanding the MPTP toxicity and mechanism of nigrostriatal degeneration has helped discover many compounds and stem cell-based approaches to alleviate or prevent the symptoms (Langston 2017; Simon et al. 2019; Park and Chang 2020; Pu et al. 2023). Human NSCs (hNSC) were implanted in monkeys treated with MPTP at the site of bilateral caudae and right SN which reduced the number and size of tyrosine hydroxylase-positive cells comparable to non-MPTP-treated controls(Bjugstad et al. 2005). Treatment protocol for accidental exposure to MPTP includes the immediate use of MAO inhibitors such as selegiline and rasagiline, to prevent the formation of MPTP-derived toxic metabilities.

Re-establishing the lost connections using stem cells

The cell replacement strategy focuses on re-establishing the lost connection due to degenerative changes. The adult CNS has limited intrinsic ability to regenerate, and stem cell-based therapies are being developed to surpass this hurdle. Regeneration or replacement of the lost neurons, re-establishment of the neural connections, and functional recovery are the key objectives of cell replacement therapy in neurodegenerative disorders (Okano 2011). The cell replacement therapy depends on the surviving transplanted cells extending their neurites and making new connections in the grafted area. However, the process is slow and may take several months to make functional changes (Morizane 2023). When the degeneration occurs in PD, microenvironment changes occur in the SN, involving the neurons, glial cells, endothelial cells, and peripheral immune cells. The neuroinflammatory cascade in PD is similar to other neurodegenerative conditions, making it difficult for any regenerative approach to succeed (Hirsch et al. 2005). It has been reported that the neural stem cells when used for cell replacement therapy integrate into the host tissue and promote rescue of the host cells by altering the host environment. Another observation from this study is that the neural stem cells migrate well in the aged brain rather than in the adult brain, possibly as a response to degeneration and ageing. Similarly, spontaneous differentiation of neural stem cells was observed in the MPTP-treated brain with impaired DA neurons. At the same time, there was no such spontaneous differentiation in the intact aged or adult brain. These observations suggest that the exogenous neural stem/progenitor cells may be used to

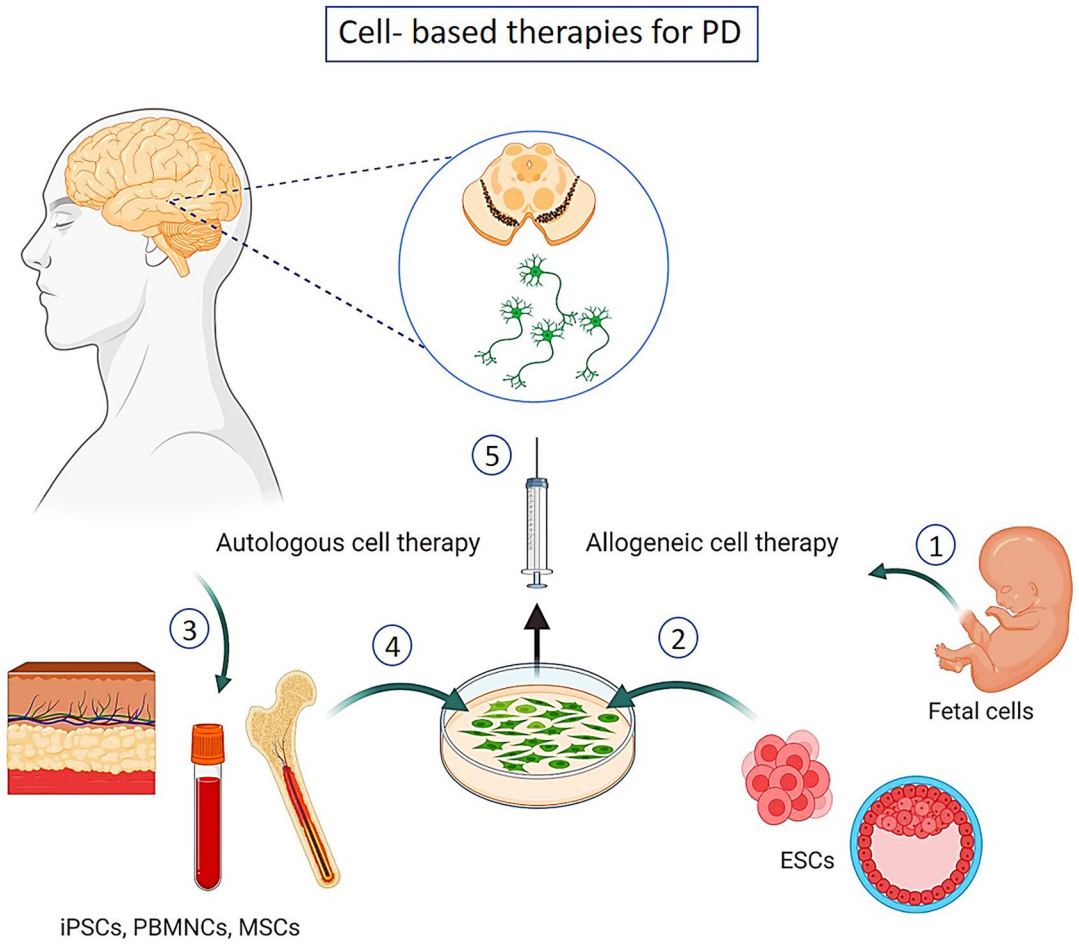

Fig. 3 An overview of cell-based therapies for PD. Allogeneic cell therapy involves 1. direct grafting of foetal neural tissue to the PD lesion or 2. transplantation of embryonic stem cells (ESC)-derived DA neurons or progenitors to the patient. In autologous cell therapy 3. adult stem cells (MSCs, PBMNCs, etc.) or blood/skin fibroblast-derived iPSCs are collected from the PD patient. 4. Autologous stem cells are differentiated into DA neurons or neural progenitors in vitro. 5. Adult stem cells/iPSC-derived neural cells are transplanted back to the patient for integration into the SNc (image generated in Biorender)

promote the endogenous regeneration of the host tissue. In this strategy, genetically manipulated exogenous stem cells may deliver the trophic factors and molecules that could alter the host tissue microenvironment to rescue the endogenous cells and regain their functionality.

Allogeneic cell replacement therapy

Foetal cells

Replacement of lost DA neurons for restoring the neural circuits with foetal tissue was the first cell therapy approach in PD (Li and Li 2021). Foetal tissues were obtained from spontaneous abortions, stillbirths, surgical procedures associated with ectopic pregnancy, and elective abortions. Foetal tissues have a greater number of stem cells and are less immunogenic, with higher proliferation than adult tissue-derived cells (Ishii and Eto 2014). In the late 1980s, the ventral mesencephalic tissue from elective abortions was utilised in the human cell therapy trials in PD. Researchers were able to implant these cells into the caudate and putamen regions of the brains of immunosuppressed PD patients without causing any significant complications (Lindvall et al. 1988). The transplantation of foetal cells improved dopamine synthesis and motor symptoms, bradykinesia, and rigidity in one of the two patients (Lindvall et al. 1990). In a similar study, a non-immunosuppressed PD patient was implanted with foetal tissue stereotactically throughout the caudate and putamen regions. A 1-year follow-up study demonstrated significant therapeutic benefits to the patient regarding motor symptoms, such as improved hand speed, walking speed, and a better medication response (Freed et al. 1990). Several similar studies showed promising results with the transplantation of foetal grafts; afterwards, more than 350 patients received foetal cell grafts by the beginning of the 2000s (Spencer et al. 1992; Kefalopoulou et al. 2014; Li

and Li 2021). Even though foetal grafts showed promising results, several concerns were there in their clinical translation path.

The trials with foetal cell therapy showed inconsistent results. Some patients had beneficial outcomes, while others showed no significant change in the symptoms. Some patients also exhibited significant side effects such as graft-induced dyskinesias, inflammation, confusion, and hallucination (Olanow et al. 1996). The most unexpected outcome was the development of multifocal brain tumours after intracerebellar and intrathecal injection of human foetal neural stem cells to treat ataxia telangiectasia. Characterisation of the tumour tissue revealed that the origin was from the transplanted neural stem cells, and cells from two aborted fetuses were present (Amariglio et al. 2009). Another concern in using foetal cell transplantation as a therapy for PD includes the ethical issues associated with the procurement of cells. In addition to this, the availability of foetal tissue is also a concern. These factors and the long-term safety concerns associated with foetal stem cell transplantation delay the translation of this therapy to clinics.

In the past, the relatively high number of foetal cell trials caused the adoption of insufficient precautionary measures, resulting in compromised foetal cell quality. Some studies considered only the number of transplanted cells rather than their functionality. Testing and the screening of donors were insufficient to prevent infectious diseases (Ishii and Eto 2014). The European multi-center consortium, TRANSEURO (NCT01898390), was formed in 2010 to minimise variability and improve the consistency and efficacy of dopamine cell replacement therapy. The consortium aims to improve DA cell replacement therapy in PD by improving tissue preparation, cell delivery, patient selection, and immunosuppression strategy. Another objective is to demonstrate that the DA treatment can be effective without causing side effects suchas dyskinesias, as seen with foetal ventral mesencephalic grafts. A template protocol may be standardised as a guideline for all future cell-based therapies and their ethical implications (Barker and TRANSEURO Consortium 2019; Petit et al. 2014).

Embryonic stem cells

Embryonic stem cells (ESCs) are another potential stem cell source for allogeneic cell replacement therapy in PD. ESCs are multipotent stem cells with high proliferative capacity. In contrast to foetal cell therapy, the availability of cells is not a limiting factor with ESCs. Even in the midst of ethical dilemmas surrounding ESCs, IVF surplus embryos can be obtained for cell therapy applications. In vitro differentiation of ESC to DA neurons or neural stem cells for applications in cell therapy is well studied. The embryonic patterning and differentiation of the foetal midbrain can be recapitulated in vitro using mitogens, small molecules, and signalling inhibitors to generate midbrain DA neurons (Eiraku et al. 2008; Kirkeby et al. 2012). BMP/SMAD signalling plays a vital role in developmental neurogenesis and the generation of midbrain DA neurons (Jovanovic et al. 2018). Inhibition of SMAD using dual inhibitors, Noggin and SB43154, has demonstrated robust and rapid differentiation of ESC to neural cells with approximately 80% efficiency.

Many pre-clinical studies have demonstrated the efficiency and potency of ESC-derived DA neurons or precursors to be used as a cell source for therapy in PD (Kriks et al. 2011; Doi et al. 2012; Grealish et al. 2014). The pre-clinical studies of the NCT03119636 trial reported improved motor symptoms in PD rat models without toxicity or any other adverse effects (Piao et al. 2021). The first clinical studies using ESC-derived neural stem cells are NCT03119636 and NCT02452723. These trials with neural stem cells investigated cytokine effects such as neuroprotection and suppression of inflammation (Takahashi 2021). Another clinical trial by BlueRock Therapeutics (NCT04802733) tests ESC-derived midbrain dopaminergic neurons in PD patients. However, it is still unclear if the ESCs are safe and effective for being adapted as a potent cell source for therapy.

The safety of ESC-based cell therapy depends not only on the behaviour of the cells in vivo, but also on the in vitro differentiation protocols. A previous pre-clinical study reported that human ESC-derived DA neurons transplanted into a rat PD model developed teratomas when the in vitro differentiation protocol was 16 days long. Teratoma formation was not observed when the protocol was either 20 or 23 days. These results suggest that prolonged in vitro differentiation is safer than short differentiation protocols (Brederlau et al. 2006). Another study also showed highly malignant teratocarcinoma formation at the site of implantation of mouse ESC-derived cells, irrespective of whether the cells were pre-differentiated or not (Erdo et al. 2004).

In addition to the ethical issues and donor cell availability, allogeneic transplantation is also associated with the need for long-term immunosuppression. Even though the stem cells are considered less immunogenic, transplantation without HLA characterisation and matching causes immune conflicts (Kot et al. 2019). Immune reactions following the allogeneic transplantation cause transplant rejection and could also affect the differentiation of the transplanted progenitor cells such as neural stem cells (Ideguchi et al. 2008). Calcineurin inhibitors or mTOR inhibitors are commonly used for immunosuppression. But, long-term use is associated with complications such as hepatotoxicity, nephrotoxicity, hypertension, and immune suppression (Master et al. 2007).In addition, the issues with tissue availability, ethical dilemma, and tumourigenicity make translating allogeneic cell therapy difficult, leaving autologous cell therapy as a viable option. The only requirement in autologous cell

therapy is an accessible source of stem cells or neural cells, which could be transplanted to the lesion site to replace the lost neurons or promote adult neurogenesis in the PD brain. Induced pluripotent stem cells (iPSCs), adult stem cells, and induced neurons are the most studied cell sources that may be used for autologous cell replacement therapy.

Autologous cell replacement therapy

Induced pluripotent stem cells (iPSCs)

The iPSCs are pluripotent stem cells which could be generated from adult fibroblast cells by stable transduction with transcription factors, Oct3/4, Sox2, c-Myc, and Klf4 (Takahashi and Yamanaka 2006). iPSC technology enables the production of ESC-like pluripotent stem cells from the patient's blood or skin cells. iPSC-based cell therapy has reduced the risk of transplant rejection and immunosuppression, as observed in allogeneic transplantation. The long-term efficiency and safety of DA neurons derived from iPSCs have been demonstrated in various pre-clinical studies (Hallett et al. 2015; Wang et al. 2015; Wakeman et al. 2017; Kikuchi et al. 2017; Doi et al. 2020). However, the long-term safety of viral-based transduction protocols warrants further confirmation. The differentiation of iPSCs to neural cells can be achieved using Noggin and SB431542 via dual SMAD inhibition without using viral vectors. However, such a differentiation process is tedious and further induction with molecules such as BDNF, ascorbic acid, sonic hedgehog, FGF8, GDNF, TGF-β3, and cyclic-AMP is necessary to induce the differentiation of iPSCs to mature midbrain DA neuronal subtype (Chambers et al. 2009). Different differentiation strategies and protocols are being developed to induce the differentiation of iPSCs to dopaminergic neurons (Grow et al. 2016; Fedele et al. 2017; Rakovic et al. 2022).

In the USA, a patient with idiopathic PD was transplanted with autologous iPSC-derived midbrain DA neurons into both hemispheres of the putamen region. iPSC-derived grafts delivered to the left and right sides of the putamen survived for 24 and 18 months, respectively. Moderate improvements were demonstrated in the clinical measures of PD symptoms 18–24 months after implantation (Schweitzer et al. 2020). Several clinical trials are currently in progress to evaluate the safety and efficacy of iPSC-derived dopamine neurons in treating Parkinson's disease. The Kyoto trial (UMIN000033564) is the first iPSC-based trial in PD. The iPSCs-derived DA progenitors were transplanted into the corpus striatum of PD patients to replace the lost DA neurons. The safety and efficacy of the clinical grade DA precursors were initially tested in immunodeficient mice, 6-OHDA rats, and MPTP monkeys (Takahashi 2019, 2020, 2021). iPSCs have a better reputation regarding safety and acceptability when compared to ESCs. iPSCs technology generally involves retroviral or lentiviral transduction, which could cause insertional mutagenesis, posing a risk for clinical translation. However, several integration-free methods, such as plasmids, Sendai virus, adenovirus, and synthesised RNAs/proteins, are currently being adopted to reduce the adverse effects (Yamanaka 2012). The safety and efficacy of iPSCs remain a question until the clinical trials are completed.

Adult stem cells

Adult stem cells exist in almost all tissues and are crucial for homeostasis. These cells can proliferate and differentiate into cells of a particular lineage based on intrinsic and extrinsic signalling cues. Most adult stem cells are tissue specific and stay quiescent. Autologous stem cell-based therapy utilises the differentiation potential of stem cells residing in the accessible adult tissues to obtain the desired cell types. Adult stem cells can be programmed to differentiate into desired cell types in a controlled in vitro environment. One of the most researched adult stem cells for application in cell therapy is mesenchymal stem cells (MSCs). MSCs are stromal cells that have multipotency and self-renewal properties. They could be isolated from bone marrow, adipose tissue, dental tissue, and menses blood. MSCs are easy to acquire in large numbers with minimally invasive procedures, making them a reliable cell source for cell therapy in elderly patients (Ding et al. 2011). The bone marrow-MSCs (BM-MSCs) have been shown to protect against the progressive loss of DA neurons induced by protease inhibitor MG-132 in both in vitro and in vivo conditions (Sun et al. 2006; Park et al. 2008). The exosomes derived from MSCs might function as biological nanoparticles and exert therapeutic effects in PD (Vilaça-Faria et al. 2019). MSCs have advanced to the stage of clinical trials for use in Parkinson's disease (Table 1).

Researchers use several strategies to induce the differentiation of MSCs into DA neurons in vitro (Table 2). Directed differentiation using signalling molecules or small molecule inhibitors is more reliable, as the genetic manipulation strategies may have long-term side effects. One of the least studied yet potential sources of autologous cell therapy is peripheral blood mononuclear cells (PBMNCs). It has been shown that PBMNCs are capable of neural differentiation, but they are primarily used for generating iPSCs for autologous cell therapy (Tara and Krishnan 2015; Generali et al. 2019). A similar study demonstrated the directed differentiation of rat PBMNCs into DA neurons with approximately 90% efficiency (Prakash et al. 2023). Blood is one of the most accessible cell sources, and developing a strategy based on peripheral blood may enable autologous cell therapy with minimal discomfort to the patient.

Age is a critical factor to be considered when developing an autologous cell-based therapy for PD. Some autologous

Table 1 List of pre-clinical studies using autologous cells for cell therapy in PD

Cell type	Year	Differentiation condition	Type of delivery	Number of cells transplanted	Transplanted animal
Human nasal mucosa	2008 (Murrell et al. 2008)	Cells cultured in wells coated with collagen IV, or poly-L-ornithine plus laminin. Media—DMEM/ITS with or without GDNF	Stereotactic injection into the striatum	37,000–210,000	SD rats
BM-MSC	2013 (Ren et al. 2013)	MSCs were infected with GDNF-encoding lentivirus (differentiation not shown)	3 sites in the caudate nucleus, 3 sites in the putamen, and 1 site in SN	10^6–10^7 Cells	Cynomolgus monkeys
Autologous iPSC	2021 (Tao et al. 2021)	NBA supplemented with N2, B27, BDNF, GDNF, Ascorbic acid, cAMP, TGFβ3	Stereotaxic injection into commissural and post-commissural putamen and caudate nuclei	11–20 million	Rhesus monkey
Human iPSC derived from skin fibroblast	2020 (Song et al. 2020)	DMEM/F12 media supplemented with N2, BDNF, GDNF, TGFβ3, dbcAMP, Ascorbic acid	Striatum	1 Lakh—3 Lakh	Rat
Human iPSC from fibroblast	2015 (Hallett et al. 2015)	N2 media supplemented with SHH-N, SHH-C24II, FGF8b, FGF8a, BDNF, TGF-β3, GDNF, cAMP, and ascorbic acid. At day 21 cells passaged and cultured on a polyornithine/laminin-coated dish in the presence of BDNF, ascorbic acid, SHH, and FGF8 for 7 days then later in the presence of BDNF, ascorbic acid, cAMP, GDNF, and TGF-β3	Right putamen		Monkey
BMSC	2012 (Hayashi et al. 2013)	Transfected with a plasmid having Notch intracellular domain and cultured in an alpha-minimum essential medium having 5% foetal serum calf, forskolin, bFGF, and CNTF and later GDNF also included		14.0×10^6 cells	Cynomolgus monkey
Cortical cells	2019 (Borgognon et al. 2019)	NA	2 in the putamen and 1 in the caudate nucleus in each hemisphere	Approximately 300 000 cells in total	Macaques
iPSC from cynomolgus macaque skin fibroblasts	2013 (Cooper et al. 2012)	N2 medium, SHH, FGF8, ascorbic acid, BDNF, after 7–9 days of culture media changed to Ascorbic acid, BDNF, GDNF, TGF-β3, dcAMP	Stereotaxic injection	1 lakh—2 lakh	Cynomolgus monkey

Table 1 (continued)

Cell type	Year	Differentiation condition	Type of delivery	Number of cells transplanted	Transplanted animal
Human iPSC from dermal fibroblast	2010 (Hargus et al. 2010)	N2 medium, SHH, FGF8, ascorbic acid, and BDNF, after 7–9 days of culture media changed to ascorbic acid, BDNF, GDNF, TGFB3, and dcAMP			
Human BM-MSC and Rat BM-MSC	2008 (Levy et al. 2008)	NA	Subcutaneous injection	30 lakhs	SD rats
Human BM-MSC and Rat BM-MSC	2004 (Dezawa et al. 2004)	Cells tranfected with Notch intracellular domain. Cells cultured in α-MEM media containing FSK, bFGF, CNTF, and GDNF	Injection into striatum	1 lakh	Wistar rats
Human umbilical mesenchymal stem cells	2006 (Fu et al. 2006)	Neuronal conditioned media obtained by growing cells from brain tissue in DMEM media along with SHH, and FGF8 growth factor	Stereotaxic injection into the striatum	1 lakh	SD rats
Human buccal fat pad stem cells	2017 (Takahashi et al. 2017)	Neural induction media supplemented with MEM-NEAAs, glutamate, all trans-retinoic acids, ascorbic acid, insulin, dexamethasone, progesterone, estradiol, neural growth factor-1, and thyroxine (T4)	Microinjection cannula into the right side of the MFB	4 lakhs	Wistar rats

Table 2 Clinical trials: autologous cell therapy in PD

Official title	Type of cell	No. of participants	Mode of delivery	Start date	End date	Institute	Clinical trial identifiers	Current status
To Study the Safety and Efficacy of Bone Marrow-Derived Mesenchymal Stem Cells Transplant in Parkinson's Disease(Arias-Carrión and Yuan 2009)	Bone marrow-derived stem cell	5	Stereotactic injection into striatum	July 2022	April 30, 2012	Jaslok Hospital And Research Centre, Mumbai, India	NCT00976430	Terminated (could not recruit adequate no.of patients in the set time frame)
Clinical Study of the Safety and Efficacy of Autologous Neural Stem Cells in the Treatment of Parkinson's Disease	Ips-neural stem cells	10	Intravenously	February 1, 2019		Allife Medical Science and Technology Co., Ltd	NCT03815071	Unknown
Develop and Implement a Method of Parkinson's Disease Therapy Using Cell Technology(Boika et al. 2020)	Autologous mesenchymal stem cells	50	Intravenous, tandem (intranasal + intravenous)	July 1, 2017	December 31, 2021	Belarusian Medical Academy of Post-Graduate Education	NCT04146519	Recruiting
A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of Autologous HB-adMSCs vs Placebo for the Treatment of Patients With Parkinson's Disease	Autologous mesenchymal stem cells	50	Intravenously	June 28, 2021	28 May-2023	Hope Biosciences Stem Cell Research Foundation	NCT04928287	Active, not recruiting
An Intermediate Size Patient Population Expanded Access IND to Evaluate the Safety of Autologous HB-adMSCs for the Treatment of Patients With Parkinson's Disease	Adipose-derived stromal cells (ASC)	10	Intravenous	June 1, 2021	3/2/2023	Hope Biosciences Stem Cell Research Foundation	NCT04772378	Available

Table 2 (continued)

Official title	Type of cell	No. of participants	Mode of delivery	Start date	End date	Institute	Clinical trial identifiers	Current status
Continuation of a Pilot Study to Evaluate the Safety and Feasibility of Implanting Autologous Peripheral Nerve Grafts in Subjects With Parkinson's Disease Undergoing Deep Brain Stimulation Surgery and Treatment(Cg et al. 2018)	Autologous Peripheral Nerve Graft	70	Surgical implantation of autologous peripheral nerve graft into the substantia nigra, basal forebrain, putamen, and/or STN of participants with Parkinson's disease that are undergoing deep brain stimulation (DBS	February 2022	September 2022	University of Kentucky	NCT02369003	Active, not recruiting
Neurologic Bone Marrow Derived Stem Cell Treatment Study (Weiss and Levy 2016)	Autologous bone marrow-derived stem cells (BMSC)	500	Intravenous and Intranasal BMSC	Jun 16	Jul 24	MD Stem Cells	NCT02795052	Recruiting
Potential Use of Autologous and Allogeneic Mesenchymal Stem Cells in Patients With Multiple System Atrophy	Adipose mesenchymal stem cell	15	Injection	05 Oct-20	05 Oct-21	Indonesia University	NCT04876326	Recruiting
Use Of Autologous Stem Cell Use In Neurological Non-neoplastic Disorders And Disease	Adipose-derived tissue stromal vascular fraction (tSVF	300	Intravenous	01 Jan-20	01 Jan-23	Regeneris Medical	NCT03297177	Not yet recruiting

stem cells, such as MSCs, show a negative correlation between age and proliferation. MSCs isolated from adipose tissue or bone marrow of older patients have lower proliferation rates and may not grow well in vitro. Similarly, mitochondrial dysfunction has also been linked to ageing in mesenchymal stem cells (Marędziak et al. 2016; Fričová et al. 2020). Since PD is usually a late-onset disorder, the age-related decline of the proliferation potential of MSCs may narrow the clinical translation path. iPSCs have an advantage over MSCs or any autologous stem cells that the generation of iPSCs by expression of reprogramming factors improves the cellular and physiological ageing signs (Ocampo et al. 2016).

iDA cells

Stem cell-derived DA neurons may include a small percentage of proliferating cells and may cause tumour formation when transplanted. Mitomycin C can selectively remove the proliferating cells from the differentiated cell population. This method can be used to select the non-proliferative cell population for transplantation (Hiller et al. 2020). An approach used in the Kyoto trial was to sort and enrich the DA progenitors using CORIN, a floor plate cell surface marker. The CORIN sorting removes unwanted immature cells, further improving the safety and quality of DA cell therapy (Kikuchi et al. 2017). Alternatively, methods have been developed to directly convert adult somatic cells into dopaminergic neurons (iDA) by expressing various transcription factors such as mash 1, nurr 1, and lmx1a (Caiazzo et al. 2011). The generation of iDAs does not involve passing cells through the undifferentiated state. It is a direct conversion method, thereby reducing the probability of tumour formation due to uncontrolled proliferation. Even if the stem cell stage is bypassed with direct conversion, the viral vectors generally used in direct conversion pose risks in the long run.

Cell replacement therapy also carries the risk of host-to-graft transmission of the α-synuclein pathology. In PD patients who received foetal tissue grafts, a disease pathology spread from the host brain was observed in 11–12% of the dopaminergic neurons grafted (Li et al. 2016). Similarly, the transmission of α-synuclein pathology in the form of the inclusion of phosphorylated α-synuclein from host cells to ESC-derived dopaminergic neurons was observed in a 6-OHDA rat model (Hoban et al. 2020). The transplanted cells in the PD brain may differentiate, migrate, and integrate into the affected areas immediately after transplantation. But the endocytosis and deposition of extracellular synuclein derived from host neurons may inhibit the long-term benefits of graft. Previous studies have demonstrated this effect in both in vivo and in vitro with mouse cortical neural stem cells and primary neurons (Desplats et al. 2009; Hansen et al. 2011). Even though some clinical studies report the beneficial effects of cell-based therapies in PD, follow-ups are needed to confirm the reliability of long-term benefits.

Gene therapy

Another potential treatment option for PD is gene therapy. This strategy can be used to introduce a gene into the cell, which can replace the faulty or missing gene/s associated with the disease. Gene therapy may be used in PD treatment to restore the neurocircuitry, deliver trophic factors, and promote dopamine synthesis in the nigro-striatal region. Adeno-associated vector (AAV) and lentiviral vectors (LVV) are the two vectors that have the potential for clinical translation. The AVV have gained attention over the past years for in vivo gene therapy as they do not integrate into the patient genome and have only low immunogenicity (Hitti et al. 2019; Buttery and Barker 2020). Glutamic acid decarboxylase (GAD) is a target gene that is used to improve neurocircuitry. GAD enzyme is rate limiting in the production of the neurotransmitter GABA. The GABA activity towards the subthalamic nucleus and their targets in basal ganglia circuitry is often affected in PD. A previous double-blinded, randomised study investigated the modulation of GABA production by delivery of AAV2-GAD in the subthalamic nucleus of subjects with advanced PD. The positive results suggested the continued development of the strategy as an effective treatment (LeWitt et al. 2011). Glial cell line-derived neurotrophic factor (GDNF) is essential for DA neuronal outgrowth and survival. It has been reported that the GDNF gene therapy may promote DA neuronal graft survival, plasticity, sprouting, and innervation into the recipient's target nuclei. It was also associated with augmented activation of striatal neurons and DA metabolism depending on the time of gene delivery (Zheng et al. 2005; Gantner et al. 2020). Since the half-life of GDNF is low and it does not cross the blood–brain barrier (BBB), a gene therapy approach based on viral vectors is used to deliver this growth factor to the brain (Pandey and Singh 2022). The first clinical use of the AAV2-GDNF vector co-infused with gadoteridol (an MRI contrast agent) into the bilateral putamina of adult PD patients using MRI guidance reported safe and well-tolerated gene delivery. The results also showed a neurotrophic effect of GDNF on DA neurons (Heiss et al. 2019). Another strategy is the stable transgene expression of the aromatic amino acid decarboxylase (AADC) gene. AADC is crucial for the conversion of exogenous and endogenous L-dopa to dopamine in the nigro striatal region. L-Dopa therapy gets less effective over time due to a decline in the AADC enzyme, which leads to the necessity of initiating efforts to increase the expression of AADC through gene therapy. (Bankiewicz et al. 2006). By increasing AADC expression in

the putaminal neurons, medically administered L-Dopa may be converted to dopamine (DA) faster, thereby improving efficiency (Bankiewicz et al. 2006; Muramatsu et al. 2010). An open-label study of ten patients with advanced PD, who received bilateral infusions of AAV2-hAADC vector to the putamen, indicated an improved L-Dopa response in the first 12 months with slow decline in subsequent years (Mittermeyer et al. 2012). Another study spanning 36 months reported short-term safety and efficacy with AADC AVV therapy in patients with advanced PD (Christine et al. 2022). AADC therapy can only improve the conversion of L-Dopa to dopamine by restoring enzyme activity, but does not help to restore endogenous dopamine. Consequently, certain clinical studies test the combined delivery of tyrosine hydroxylase (TH), AADC, and GTP cyclo hydroxylase 1 (GCH). Transduction with GCH converts the non-DA cell to DA neurons, restoring endogenous DA production (McFarthing et al. 2019). Several other approaches, such as AVV-based therapies using neurturin, a homologue of GDNF, CDNF, and LV-based AADC, TH, and GCH1, were also studied (Palfi et al. 2014; Elkouzi et al. 2019).

In vivo gene therapy using AAV is approved in the USA and Europe and may gain more traction in the coming years (Axelsen and Woldbye 2018; Commissioner 2020). However, in cases where high-dose AAV therapy is needed, immune complications could arise and may even require immune suppression (Ertl 2022). Similarly, potential side effects, such as insertional mutagenesis and genotoxicity, must be considered with LV therapy.

Microbiome–gut–brain axis and PD

Recent research has connected gut microorganisms to the aetiology and symptoms of PD. These studies highlight the importance of gut microbiota (GM) in modulating neurodegenerative disorders (Singh et al. 2022). Gastrointestinal symptoms such as constipation, drooling, dysphagia, stomach pain, dyspepsia, and faecal incontinence are frequently seen in PD patients (Omotosho et al. 2023). Constipation is the most prevalent gastrointestinal symptom in PD, affecting up to 80% of people with the disease. Constipation can be observed in PD patients before developing motor symptoms (Su et al. 2017). This recent finding supports the Braak hypothesis, stating that α-syn first causes intestinal lesions and disrupted the enteric nervous system. It further causes Lewy body production in enteric nerves, which then acts on the vagus nerve to reach the substantia nigra and striatum and ultimately induces the development of PD (Braak et al. 2003b). According to recent research, transplanted cells appear to target the gut–brain axis by reducing the inflammatory response in the gut and preventing neurodegenerative cell death cascades in the brain. Intravenous cell-based therapies in α-syn expressing transgenic mice indicated a reduction in inflammatory microbiota, cytokines, and α-syn in both the gut and brain. The treatment also enhanced motor functions with a reduction in the death of dopaminergic neurons in the substantia nigra (Lee et al. 2022, 2023). Another study showed that patients with PD had significant variations in the gut microbiome. A significant reduction in the levels of Prevotellaceae, Faecalibacterium, and Lachnospiraceae and an increase in the levels of Bifidobacteraceae, Ruminococcaceae, Verrucomicrobiaceae, and Christensenellaceae were observed in PD patients (Shen et al. 2021). This study concluded that the ecological imbalance of these gut microbiota might cause impairment in short-chain fatty acid (SCFA) production, lipid metabolism, immune regulation, and intestinal permeability which in turn contributes to the pathology of PD. Curcumin administration improved gastrointestinal and intestinal barrier dysfunctions, decreased gut microbial dysbiosis, altered carbohydrate metabolism, corrected SCFA profiles, decreased dopaminergic neuron loss, and alleviated motor impairments in MPTP-induced mice (Cai et al. 2023). Srivastav et al. showed that a probiotic mixture containing LGG, *B. animalis lactis*, and *L. acidophilus* raises the level of butyrate and protects the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity by increasing the butyrate level (Srivastav et al. 2019). Probiotics, psychobiotics, prebiotics, synbiotics, postbiotics, faecal microbiota transplantation, and dietary changes can all affect the gut microbiota, which can be considered viable diagnostic and treatment targets for PD (Hashish and Salama 2023). Hence along with other therapeutic strategies for PD like cell transplantation, gene therapy, DBMs, and levodopa–carbidopa therapy, restoring eubiosis and homeostasis in patients' gut by the use of prebiotics, probiotics, or faecal matter transfer might be more impactful in the fight against Parkinson's disease.

Conclusion

Currently, patients and clinicians rely on detailed clinical assessments for the diagnosis of PD. Patients heavily rely on long-existing medications such as L-DOPA replacement therapy for the management of PD. In the case of advanced PD, invasive surgeries such as brain stimulation are done on patients to improve their quality of life. All current approaches are focused on symptomatic treatment rather than reversing or providing a cure for the disease. Even though cell-based therapies hold promise for treating PD, there are several untoward obstacles along the way. The most crucial part is obtaining the correct functional neuronal subtype from in vitro differentiation of stem cells. The long-term safety and efficacy of cell-based therapies are the primary concern that must be addressed before adopting such

therapies in the clinical realm. Although various clinical and pre-clinical studies have established the potential for using cell-based therapies for the treatment of PD, the large-scale production of clinical-grade cells and the ethical dilemma surrounding the usage of cells remains a bottleneck. Despite existing challenges, advancing translational research in the field will bring such therapies to fruition in the foreseeable future.

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Declarations

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