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Stem Cell Therapy, Adaptive Deep Brain Stimulation and Personalized Medicine in Parkinson Disease: An Updated Review

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Abstract

Background: Parkinson disease (PD) is a developing neurodegenerative disorder with motor and non-motor symptoms for which conventional dopaminergic treatment has a limited long-term efficacy. In the past few years, novel stem cell treatment modality, adaptive deep brain stimulation (aDBS) and personalized medicine are offering additional options for effective and long-term treatment.

Objective: The current work represents a revised synthesis of emergent therapy approaches in PD including interventional strategies based on the use of stem cells, adaptive DBS technology and personalized medicine approaches to improve clinical outcomes in PD patients.

Methodology: Clinically and analytically relevant data from 2015 to 2025 was systematically reviewed using PubMed, Scopus and Web of Science peer reviewed articles and clinical trials or experimental studies related to the included clinical study questions. To illustrate this new field of research, we reviewed studies on the efficacy, safety, patient selection and translational potential of treatments based on scientific research.

Results: Stem cell transplantation seems to be a good candidate for replacement of dopamine neurons and a number of phase I & II clinical studies are showing improvement of motor score. Interestingly, we found that the adaptive DBS based on continuous evolution of neurophysiological biomarkers was superior to conventional DBS in terms of both suppression of motor fluctuations and suppression of side effects. Digitalization, genomics, imaging, and precision medicine: Digitalization of healthcare has resulted in new approaches to treating the patients, highly personalized, to improve the response rate and disease control.

Conclusion: Stem cell therapy, adaptive DBS and personal medicine, when used together, are complementary and synergistic tools in the treatment of PD. Together they could transform clinical practice in the future by delivering patient specific, durable, enhanced therapeutic outcomes. More information from larger and more rigorous studies and reviews of long-term safety however is still pending.

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1. Introduction

Parkinson disease (PD) is the second leading neurodegenerative disorder worldwide and is characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta with a consequent loss of dopamine in the striatum. Clinically, it is defined by a combined motor symptomatology (bradykinesia, rigidity, tremor and postural instability) with an enormous variety of non-motor manifestations such as cognitive deterioration, depression, sleeping disorders, and autonomic dysfunction.

Given the heterogeneity in clinical characteristics and course of PD, this disease should be considered not only as a disease of the motor system but as a multisystem disease with a great impact both socially and economically. PD is found in more than 10 million people worldwide and its prevalence has been estimated to be 1-2% in people over the age of 65 years and in some countries its prevalence reaches over 4% for those over 80 years [1]. PD is one of the fastest increasing neurological disorders and incidence correlates with aging populations, and it is estimated that the number of patients with PD will double by 2040. Prevalence varies widely, it is higher in developing countries, which may be due to environmental exposures, lifestyle factors and improved ability and availability of the population for diagnosis. PD accounts for a considerable health burden, and DALYs attributable to PD increased more than eightfold from 1990 to 2019. In addition to physical disability, the progressive loss of quality of life, caregiver burden and health costs burden families and the health care system.

Although the symptomatic management of PD has improved, PD itself is an incurable disease and with the progressive nature of the disease, increasing disability inevitably ensues. Standard treatments, in particular levodopa and dopamine agonists, can provide excellent relief from motor symptoms in patients in the early stage of the disease and do not have an effect on neurodegeneration [2]. Traditional dopamine agonist treatment is complicated by motor fluctuations and dyskinesias, levodopa is associated with motor fluctuations and dyskinesias and malignant hyperpyrexia, dopamine agonists are associated with impulse control disorders and neuropsychiatric side effects. Background and aim Deep brain stimulation (DBS) of the subthalamic nucleus or globus pallidus internus has improved outcome for advanced PD but is still limited by invasiveness, static stimulation parameters and individual variability. Further, current treatment paradigms don't account for the presence of non-motor symptoms that are often refractory to dopaminergic therapy and remain a primary symptom in many patients. Pharmacological approaches for PD are generally focused on dopaminergic deficiency and ignore the multifactorial pathology of PD, including mitochondrial dysfunction, oxidative stress, protein aggregation and neuroinflammation [3]. While motor control is enhanced with the DBS, it does not alter the disease process and patient selection is critical. Interindividual variation in therapeutic response also underlines the inadequacy of a one fires one kills approach. Therefore, novel therapeutics targeting mechanisms and enabling individualized treatment to reduce the cardiovascular morbidity associated with the long-lasting treatment-related complications and disease progression are needed. New therapeutic modalities have been enabled by recent advances in neuroscience, molecular biology and bioengineering. Stem cells therapy offer a promise to replace lost neurons (dopaminergic neurons) and could be used as a neurotrophic agent, Adaptive DBS (aDBS) that relies on neurophysiological biomarkers captured by brain recording to optimize stimulation parameters in a dynamic way to reduce side effects while increasing efficacy [4]. However, considering the potential of personalized medicine through the availability of genomic, biomarker, and digital health data, new treatment approaches based on patient profiles are possible. Together, these new approaches fill a gap in the disease modifying and precision targeted therapeutics available for PD [5].

In this timely overview, we combine recent efforts in the field of stem cell therapy, adaptive DBS and personalised medicine for PD, describing the mechanisms of therapy, clinical evidence, translational challenge and future perspectives. For example, rapid advances in neuroscience, molecular biology and bioengineering are heralding new sophisticated therapeutic modalities and it is likely that the most effective therapeutic outcomes will be those that integrate the above advances [6]. Stem cell therapy can successfully be used to substitute lost dopaminergic neurons or for neurotrophic support. Adaptive deep brain stimulation (aDBS) system is a real-time system that utilizes neurophysiological biomarkers using which the stimulation parameters can be optimized to achieve optimum efficacy with minimum side effects. On the other hand, personalised medicine can promise a patient centred therapy based on genomic, biomarker and digital health data. Altogether, these new approaches provide solutions to the, as yet unmet, need for precision therapeutics and disease-modifying therapies for PD. In today's review, we integrate recent advances made in stem cell therapy, adaptive deep brain stimulation (DBS) and personalized medicine for Parkinson disease (PD) according to their mechanism of action, clinical evidence, translational obstacles and opportunities [7]. By detailing the potential, synergistic way these new technology enhancing innovations could work together, we present a future outlook for the next generation of PD therapeutics that has the potential to revolutionize the future of treating patients.

2. Stem Cell Therapy in Parkinson Disease

The scientific rationale behind transplantation of stem cells for the treatment of Parkinson's disease (PD) is based on the replacement of lost populations of dopaminergic neurons that are lost in the natural course of the disease. Because of their proliferative potential and ability to generate multiple lineages, stem cells are a potential source for both replacement of lost neurons as well as providing trophic support or modulation of the neuroinflammatory response to trauma to support endogenous repair [8]. Given the recent success of human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs), there are many emerging approaches to cell replacement and modulation for diseases. In preclinical models, transplantation of stem cell-derived dopaminergic neurons has led to improvement in motor function, normalization of striatal dopamine levels, integration of host circuitry and formation of synaptic contacts [9]. Importantly, iPSCs derived from somatic cells of a patient's own body remove the ethical issue associated with embryonic sources and eliminate the danger of immune rejection. Finally, recent improvements in cell differentiation protocols permit production of highly pure populations of dopaminergic neurons with less risk for tumorigenesis and aberrant acquisition of fates [10].

The transition to clinical translation of stem cell therapy has gained speed and initial-phase clinical trials are reporting results that look promising from safety and feasibility studies. For instance, graft survival and a beneficial motor outcome without serious adverse effects were reported by transplantation of hESC derived dopaminergic progenitor cells into PD patients [11]. Similarly, autologous mobilized iPSC derived grafts have proven to integrate well in pilot studies in humans and therefore point towards a long-term feasibility of patient-specific cell replacement strategies.

However, we are still a very long way from that. However, the relative variability of graft survival, functional integration and long-term efficacy still requires optimization of cell preparation, of delivery techniques and of immune modulation strategies. The ability to control unlimited proliferation and/or differentiation is of utmost importance [12]. Further, there continue to be ethical and regulatory challenges to widespread clinical use, particularly when embryonic sources are used. Overall, SC can be considered a novel approach to the treatment of PD based on the concept of targeting the root of neuronal loss. And while we're still in the process of unraveling some of the major diseases that can be cured with this approach, stem cell biology, transplantation regimens, and clinical trial design are advancing in ways that are incrementally adding weight to the therapeutic potential of the technique [13].

2.1. Therapeutic Potential of Stem Cells

Stem cell therapy in Parkinson disease (PD) has as its ultimate objective the replacement of the lost dopaminergic neurons of the substantia nigra and the recovery of the striatal dopamine transmission, therefore treating the essential mechanism and no longer the symptoms. Human pluripotent stem cells (hPSC), including embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), have been reported to differentiate into midbrain dopaminergic neurons and form synaptic connections with the host neural circuits [14]. In preclinical models such neuronal replacement has been shown to improve motor coordination, reduce bradykinesia, and increase striatal dopamine concentration towards physiological levels. In addition to cell replacement, the stem cells regulate their host neurons in a paracrine, therefore neuroprotective, way. Together with brain-derived nervous aspect element (BDNF), glial telephone collection collection line-derived nervous aspect element (GDNF), and vascular endothelial development factor (VEGF), they secrete a number of trophic elements that facilitate the survival and function of remaining neurons, regulate neuroinflammation, and enhance synaptic plasticity [15]. In particular, mesenchymal stem cells (MSCs) have been shown to reduce microglial activation and pro-inflammatory cytokine secretion, therefore reducing the occurrence of neurodegenerative cascades.

Furthermore, we report that the stem cells are able to influence the disease microenvironment through inducible angiogenesis and by facilitating the endogenous neural progenitor cells, which might enhance the repair strategy from inside brain. Demands around gene-edited stem cells are increasing as it allows the correction of genetic mutations in patient specific stem cells and can offer personalized therapeutic treatment. From this point, not only transplantation can be performed more safely, but also the grafted cells are more functionally integrated [16].

Preclinical studies indicate that combinatorial models which combine treatments directed toward neuronal replacement with neuroprotective modulation are superior to treatments based on either strategy alone. Importantly, this therapeutic potential can be realized only if the appropriate differentiation protocols, timing, and delivery to the striatonigral pathway are correct in order to maximize connectivity [17]. In conclusion, the therapeutic effect of stem cells for PD is not restricted to the cell replacement. By neuronal integration, secretion of neurotrophic factors, immunomodulation, and support for endogenous repair, stem cell therapy is a multi-target disease modifying treatment that can work effectively on both the motor and non-motor features of Parkinson's disease. These mechanisms will need to be further optimized if translation is to be successful in the clinic [18].

2.2. Current Clinical and Preclinical Evidence

More than ten years of preclinical and dawning clinical evidence support the therapeutic potential of stem cell therapy in Parkinson's disease (PD). Transplantation of neural dopaminergic precursors derived from human pluripotent stem cells (hPSCs) into 6-hydroxydopamine (6-OHDA) or MPTP induced models of Parkinson's disease (PD) has been shown to produce significant motor recovery, dopamine replacement in the striatum, and functional connectivity into native circuits in animal models [19]. For example, in rodent studies, hESC or iPSC derived grafts persist for more than six months post-transplantation, display electrophysiological activity that is characteristic of dopaminergic neurons, and restore rotational activity in lesioned animals. Further, in non-human primate studies, grafted cells demonstrated long term survival, striatal reinnervation and ongoing improvement in movement scores that are characteristic of Parkinson disease [20]. Mesenchymal stem cells (MSCs) have been demonstrated to have additional neuroprotective effects in animal models. MSC transplantation decreases microglial activation, inhibits pro-inflammatory cytokines and promotes endogenous neurogenesis, thus delaying neurodegenerative progression. Combined preclinical studies using MSCs and neurotrophic factors like GDNF or BDNF have provided evidence for synergistic effects in terms of improved motor recovery and dopaminergic neuron rescue superior to that obtained with MSCs alone [21].

Table 1: Summary of Stem Cell Therapy Studies in Parkinson Disease

Study	Stem cell type	Model/Patient Cohort	Intervention	Key Findings	Limitations
TRANSEURO (2019)	Fetal ventral mesencephalic cells	Human PD patients	Transplantation into striatum	Improved UPDRS motor scores; graft survival	Graft induced dyskinesia; small sample
Japanese Phase I (2022)	Autologous iPSC derived neurons	Human PD patients	Striatal transplantation	Graft survival; motor improvement; no severe adverse events	Short-term follow-up; scalability
Rodent 6-OHDA models	hESC derived dopaminergic neurons	Rats	Striatal transplantation	Restoration of dopamine; improved rotational behavior	Preclinical; long-term safety unknown
Non-human primate	iPSC derived neurons	MPTP monkeys	Transplantation	Improved motor function; striatal reinnervation	Costly; translational complexity

Clinically, several early phase trials have been performed that have assessed safety and feasibility in PD patients. The European multicenter TRANSEURO trial of fetal ventral mesencephalic tissue transplantation reported long-term graft survival and subtly improved motor function, although graft induced dyskinesias also were identified as a complication [22]. More recently, trials of hESC or iPSC derived dopaminergic progenitor cells have demonstrated promising early results. For instance, a phase I study from Japan showed the long-term survival of autologous iPSC-derived grafts without significant adverse events at 24 week follow up and improvement in Unified Parkinson Disease Rating Scale (UPDRS) motor scores. Furthermore, clinical experience with graft transplants from hESCs has shown a good safety with some patients obtaining clinically significant improvements in motor function. Yet despite such progress, some issues remain that are a challenge yet to be fully addressed. Immune heterogeneity, as determined by degree of graft differentiation, graft survival and integration is one of the proposed explanations for disparity and variability of results. Embryonic origin, immunologic rejection and tumorigenicity are major concerns [23]. Finally, long-term longitudinal follow-up and further development of transplantation methods and standardization of the protocol is needed to establish safety and efficacy of this approach. In conclusion, according to early clinical studies and preclinical studies, it appears that stem cell transplantation has great promise in PD and can exert a neurorestorative and neuroprotective effect. Whilst encouraging, such findings still need to be repeated in larger cohort, controlled trials to replicate long term benefit and surmount translational barriers before widespread clinical adoption [24].

3. Adaptive Deep Brain Stimulation (aDBS)

Deep brain stimulation (DBS) has revolutionised the treatment of advanced Parkinson's disease (PD) and has demonstrated to be an effective treatment for providing substantial relief from motor symptoms including tremor, rigidity and bradykinesia. With conventional DBS, the nuclei responsible for activation of the system, the subthalamic (STN) nucleus or globus pallidus internus (GPi), which are the most frequently used are continually stimulated by electrical impulses, which contribute to restore motor function and reduce dopaminergic medication [25]. However, continuous stimulation leaves no room to detect dynamic changes in the neuronal activity or disease progression and usually leads to suboptimal treatment, stimulation-induced side-effects and unnecessary energy consumption. Adaptive deep brain stimulation (aDBS) represents an extension of standard DBS towards closed-loop systems able to adapt stimulation settings on-the-fly based on the neurophysiological signals. By detecting oscillatory activity, and in particular beta-band oscillations, from the STN, aDBS is capable of stimulating only during the occurrence of pathological neural patterns, maximizing the therapeutic effect while minimizing side effects [26]. In this way, a neural circuit can be modulated independently for each motor state of the patient.

Preclinical and early clinical studies indicate that aDBS may lead to greater reduction of motor fluctuations compared to continuous DBS. Moreover, aDBS may be associated with reduced risk of developing dyskinesias compared to continuous DBS at lower stimulation amplitudes. In addition, aDBS systems lead to increased compliance and greater safety among patients over the long-term [27]. The technology could also be integrated with wearable sensors and telemetry systems, to allow for one-on-one therapy in a natural environment. While aDBS is a promising method, the method has not been broadly adopted due to technical complexity, identification of only a subset of biomarkers and cost. Conclusions: aDBS is a first step towards precision neuromodulation in PD and towards tailoring treatment to the variability of neuronal activity and patient needs [28].

3.1. From Conventional DBS to Adaptive Systems

Deep brain stimulation of the subthalamic nucleus (STN) or the globus pallidus internus (GPi) is now considered first-line therapy for advanced Parkinson's disease (PD) with the aim of improving the motor symptoms. Continuous DBS refers to a constant frequency HFES which is not dependent on the patient dynamic neural state Although this leads to dramatic improvement of tremor, rigidity and bradykinesia, there are also some limitations to the technique [29]. Side effects of continuous stimulation include dysarthria, dysphonia, ataxia and stimulation-induced dyskinesias. Moreover, fixed stimulation does not cause motor function or disease progression to change over time in ways that make treatment challenging. However, due to high energy consumption and frequent replacement of its battery, the application of conventional DBS is also limited to long-term operation [30]. Adaptive deep brain stimulation (aDBS) has promised to be a new means to overcome these limitations. In contrast, by means of closed-loop stimulation, aDBS is able to dynamically adjust stimulation according to feedback of the neurophysiological signal and target pathological activity patterns exclusively at the moment of their occurrence. Compared to conventional deep brain stimulation (DBS) with closed loop stimulation, the approach of open-loop stimulation provides more selective and efficient neuromodulation [31]. Opportunities for the development of aDBS are provided by the fact that sensory information is able to detect local field potentials (LFPs) and oscillatory brain activity in the beta frequency range (13-30 Hz) related to the motor impairment in PD.

The adaptive systems are realized through the integration of sensing electrodes, signal processing algorithms and programmable stimulators. This allows the system to automatically increase or decrease the stimulation intensity to minimize any side effects from the stimulation while maximizing the motor outcome [32]. Previous human chronic experience has shown that aDBS can maintain or even improve motor control at lower cumulative levels of stimulation that may offer more safety & energy efficiency. Overall, the development of adaptive DBS is a paradigm shift in neuromodulation from static and generalized stimulation to dynamic stimulation and targeting specific to individual patients. By synchronizing brain activity in real time to stimulation, aDBS has the potential to increase motor symptom control, quality of life, and enable more tailored treatment strategies in Parkinson [33].

3.2. Biomarkers and Neurophysiological Feedback

Accurate neurophysiological biomarkers are used to centrally regulate the electrical stimulation in real time for adaptive deep brain stimulation (aDBS) in patients with Parkinson's disease (PD). By far the most well characterized biomarker in the STN is the reduced behavioral bradykinesia and rigidity in association with more robust and synchronized beta band oscillation (13-30 Hz) [34]. In suprathreshold cortical activity, increased beta activity is observed in patients with Parkinson's disease (PD) and has been interpreted as a sign of abnormal synchronized neuronal firing; beta can be suppressed by focal stimulation, and suppression of beta activity has been shown to improve motor function [35]. By continually measuring these oscillations, aDBS systems can adapt the stimulation parameters to optimise the therapeutic effects of the stimulation. Local field potentials (LFPs) are a rich and abundant source of biomarker information that can be gathered from implanted electrodes. The LFP based sensing enables the system to discriminate the pathological neural patterns from the physiological patterns and therefore stimulate selectively in closed loop [36]. Other emerging biomarkers, such as gamma frequency, phase-amplitude coupling or peripheral cues (electromyography, tremor frequency) could be additional sources of context to serve as guides for stimulation fit.

We believe it is critical to link neurophysiological feedback to brain stimulation outcomes by using powerful algorithms to convert raw biomarker data into imperative commands for stimulation. To help robots respond more effectively and prevent stimulation where it is not necessary, machine learning algorithms have been developed to predict motor variability and to optimize stimulation patterns. In addition, biomarker-guided aDBS is expected to reduce the risk of an excess of stimulation leading to the development of dyskinesias, dysarthria or gait impairment [37]. Early clinical experience has shown that feedback stimulation increases motor recovery while decreasing stimulation amplitudes and battery life of the feedback-controlled stimulation devices. Real-time biomarker monitoring also provides the opportunity for longitudinal measurements of disease progression (personalised treatment adaptation over time).In a nutshell, adaptive DBS is based on biomarkers (beta oscillations and LFPs) and aims to provide closed-loop neuromodulation, Adaptive DBS adjusts the stimulation based on the recording from the patient neural state in real-time [38]. This paradigm represents a substantial improvement over standard DBS with regard to efficacy, side effects, as well as individual treatment for patients with PD.

3.3. Clinical Outcomes of aDBS

Adaptive deep brain stimulation (aDBS) has been found to be clinically promising for Parkinson's disease (PD), in particular in overcoming the limitations in clinical efficacy of standard continuous DBS. By altering stimulation in real time rather than using a low intensity, fixed method, aDBS has been shown to be more effective at controlling motor symptoms while minimizing side effects of stimulation [39]. Pilot studies and some initial human subject studies have demonstrated that aDBS is very effective in reducing bradykinesia, rigidity, and tremor, and aDBS has generally been more effective than standard DBS for the treatment of motor symptoms. One study in patients with advanced PD showed that aDBS reduced Unified Parkinson Disease Rating Scale motor scores by 40-50% as compared with ~30-35% improvement with conventional DBS. Furthermore, aDBS not only resulted in greater control of motor fluctuations, but also in lesser peak-dose dyskinesias, probably because mismatch of stimulation intensity to instantaneous neural activity may be simply modified [40]. In addition, the reduced quantity of energy allowed for longer energy delivery with an increase in the number of times a patient could undergo the procedure without needing to replace devices, and would increase the overall patient convenience in addition to decreasing the procedural hazards.

Table 2: Comparative Outcomes of Conventional DBS vs Adaptive DBS

Parameter	Conventional DBS	Adaptive DBS (aDBS)
Motor Symptom Control	Moderate improvement in UPDRS	Greater improvement; dynamic modulation
Dyskinesia	Higher risk	Reduced incidence
Battery Consumption	Continuous, higher	Lower; energy-efficient
Side Effects	Speech, gait disturbances	Fewer, targeted
Patient-Specific Adaptation	No	Yes, based on biomarkers
Clinical Monitoring	Periodic clinic visits	Continuous via sensors and AI

Comparative studies have shown aDBS to provide more stable motor control over time during activities of daily living, which is more consistent with results from continuous DBS, compared with oscillatory symptoms in PD that are less tolerated with continuous DBS [41]. In addition to motor improvements, patients report perceived quality-of-life improvements including an increase in mobility a reduction in fatigue, and an increase in independence in activities of daily living. In addition, potentials for the improved function of the motor system which are confirmed by objective measurements such as kinematic analysis and acceler metry during the adaptive stimulation [42]. However there is a quite significant inter patient variability in stimulation responses which argues for highly individualized programming coupled with optimal electrode placement. Several factors are believed to affect the therapeutic response to aDBS, including disease stage, comorbidity and brain beta activity, among others. Despite the limited data available from long-term follow-up, the carriage of these benefits was sustained in follow-up of a few months to several years without an increase in the numbers of adverse events in comparison with standard DBS [43]. In conclusion, a clinical evidence base is emerging for aDBS as a potent neuro-modulatory therapy in the treatment of PD that can be implemented with stepwise stimulatory applications with incredibly flexible feedback that is adaptive to the instantaneous neurophysiological state of the patient. With improved motor function, reduced side-effects and improved QoL, aDBS marks a significant step toward precision neuromodulation in PD [44].

3.4. Technical and Implementation Challenges

Although the clinical outcomes of adaptive deep brain stimulation (aDBS) have been promising, some technical and implementation issues still exist that impede broad use for the management of Parkinson disease (PD). Closed-loop systems requiring real-time detection and interpretation of neurophysiological biomarkers are complex systems requiring fine electrode placement, high signal acquisition, and advanced signal-processing algorithms [45]. In particular, small shifts in electrode location can place a burden on the accuracy of a local field potential (LFP) recording, diminishing the performance of feedback-based stimulation. Components like contamination, noise in the signal detection and other interfering signals caused due to motion artifacts, muscle movements or other electronic devices can affect the reliability of biomarker detection [46]. How to develop algorithms that enable the identification of pathological neural patterns from physiological or artifactual signals is still a challenge. Further, individual and disease dynamics in the beta oscillation depend upon individual calibration, making standardization of aDBS protocols difficult.

Besides, device optimisation closed loop stimulator with sensing electrodes, processor and pulse generator in one hermetically sealed implantable device will be a huge challenge, because periodic battery replacement poses procedural risks and patients' burden, we need a perfect balance of an adequate battery life, and smaller size and higher computation power. Additionally, aDBS (including the DBS hardware, software, and clinical programming) is much pricier than conventional DBS, further restricting even further the patients who have access to this treatment, particularly in resource-limited settings [47]. As if all that wasn't bad enough, there's a problem in the correct choice of patients in testing. Of course, not all PD patients are suitable for aDBS patients must have different stages of disease, motor fluctuations of a certain type and no severe cognitive impairment or other comorbidities that will make surgery complicated. Long-term management requires a multidisciplinary team with the training to continue longer-term monitoring, programming, and troubleshooting. It is also influenced from a regulatory and ethical standpoint [48]. Especially in the early stages of CLNS clinical standardization, safety and reproducibility are important. Clinical trials must not only be effective, but also be safe with minimal toxicities that persist over long-term follow-up.

In conclusion, overall, while aDBS is an exciting development in the field of neuromodulation for PD, it is limited by technical complexity, expense patient specific differences and the need for long term management. While these are challenge require resolution through better biomarker identification, algorithm development, device miniaturization and training of skilled clinical teams for their application, their successful resolution will enable the widespread adoption of precision neuromodulation in PD and unlock it full potential [49].

4. Personalized Medicine in Parkinson Disease

The aim of personalised medicine in Parkinson disease (PD) is to individualise therapy based on patient-specific parameters, including genetic, biomarker and clinical phenotyping. Conventional PD management is based on a one-size-fits-all approach, variable responses and suboptimal outcome due to inter-individual patient differences in disease pathophysiology, disease progression and treatment tolerance. The recent explosion of genomics, molecular diagnostics, and computational analytics has created the conceptual basis for precision labeled neurology, where the clinician would be able to optimize each patient therapy [50]. Discovery of mutations affecting the gene products (LRRK2, PARK7, PINK1, SNCA and GBA) implicated in the pathoetiology, progression, and response to treatment of the disease has become the major focus of the molecular diagnosis approach. For example, it has been shown that mutation carriers of LRRK2 differentially respond to dopaminergic treatment and GBA mutation carriers were shown to be more sensitive to cognitive impairment and dementia. It is hoped that such genotypic information can then act as a starting point for decision making in the clinic, such as for pharmacotherapy, for modality, timing (if any) of intervention, or for eligibility to novel interventions such as stem cell transplantation or adaptive deep brain stimulation [51].

Furthermore, biomarker-based stratification can be used as a tool for precision medicine. Serum/CSF biomarkers like a-synuclein, neurofilament light chain (NfL) and inflammatory cytokines hold promise for providing new insight as *in vivo* biomarkers of disease activity and progression, and biomarkers of response following treatment [52]. Functional Magnetic Resonance Imaging (MRI) and dopamine transporters (DaT) Single Photon Emission Computed Tomography (SPECT) allow us to obtain images of the degree of loss of the nigrostriatal system and the connectivity pattern appropriate for therapeutic planning. However, from the last decade on, digital health technologies (tablet, smartphones, home digital-monitoring platform) provided the possibility of collecting objective longitudinal information with regard to changes of motor switches, tremor, and gait parameters [53]. Beyond this AI and machine learning-based analysis of the data to model the trajectory of the symptoms, it also enables a level of optimisation for parameter adjustments (drugs, neuromodulation settings etc) that can be personalized for particular risk factors.

Direct-to-consumer pharmaceutical advertising also presents opportunities for lifestyle and environmental factors to be taken into consideration in each patient's holistic care program. Because many of these risk factors are amenable to change, risk factor therapy is supplemented by pharmacological and interventional therapies to take a holistic approach to improving quality of life [54]. In conclusion, the implementation of personalized medicine is a paradigm shift in the management of PD from a generalist, reactive and disease-centred approach to care towards a more proactive, data-driven, patient-centred approach. With genome, biomarkers, and digital investigations, doctors can explore patient-specific therapies to maximize benefit and minimize side effects while effectively managing the changing disease-state. The precision paradigm developed here is at the forefront of the next generation of therapeutic approaches including synergistic combination with SC replacement and adaptive DBS and eventually will be the foundation for truly personalized care of PD [55].

4.1. Digital and AI Based Monitoring

Role of digital health technologies as tools for individualized management of PD including continuing objective assessment of PD patient motor and non-motor symptom in real life settings. For example, wearable sensors such as accelerometers, gyroscopes and inertial measurement units (IMUs) have been shown to be a useful tool for measuring tremor, bradykinesia, dyskinesia, gait impairment and postural instability. Unlike the periodic clinical exam, continuous monitoring observes change on a daily basis and reveals subtle changes in disease progression [56]. Remote monitoring of symptoms at home including motor symptoms, medication adherence and symptom severity can be achieved using home monitoring devices and smartphone applications These platforms produce vast amounts of data which can then be processed using artificial intelligence (AI) and machine learning algorithms. AI-powered analytics to assess patterns and have predictive trends for motor behavior and/or make personalized suggestions for medication adjustment or stimulation parameter change for closed-loop DBS systems

[57].

In addition to utilizing EHR and telemedicine systems, digital monitoring can be used for longitudinal monitoring and early intervention. These findings are also useful for clinicians to provide the most effective treatment protocols to reduce hospital visits and maximize patient engagement and adherence [58]. Moreover, prediction of non-motor symptoms - AI-based predictive modelling allows for earlier diagnosis of non-motor symptoms, such as cognitive decline, sleep disorders, or mood disorders and hence the opportunity for interventions to be started early. Overall, digital and artificial intelligence-based monitoring is contributing to increasing the accuracy of recommended care in PD [59]. By creating model quality and matched patient datasets with millisecond temporal resolution, these technologies not only transcend traditional clinical measurements, but also provide interpretive data for both personalized care and adaptive treatment, ultimately improving patients' outcomes and quality of life with PD.

5. Synergistic Integration of Novel Approache

Novel techniques in stem cell therapy, adaptive deep brain stimulation (aDBS) and personalized medicine make a complex and multifaceted approach to treating the complex pathophysiology of Parkinson disease (PD) [60]. Although the two approaches have different therapeutic benefits, combining them can be an effective strategy in achieving clinical outcomes by attacking disease mechanisms from different directions. Stem cell therapy addresses the underlying neuronal loss and enables neuroregeneration, in combination with the real-time optimization of neural circuit activity guaranteed by aDBS and a tailored medicine approach that is absolutely necessary to target interventions based on the individual patients' characteristics [61]. The modalities can be applied with great accuracy and in a specific order of application. For example, when transplanting stem cells into patients, aDBS can be used to stabilize motor circuitry promotion during graft incorporation with the potential of improving functional connectivity and reducing symptomatic fluctuations. In addition, the patient is selected according to genetic, biomarker and clinical profiles using unique patient identification, and the patient responsiveness to stem cell treatment or neuromodulation is specified in so doing, such stratification reduces variability related to therapeutic outcome and optimizes effectiveness and safety [62].

Further, digital health technologies and artificial intelligence (AI) analytics provide additional means for synergy between tracking patient responses across interventions. Continuous monitoring of motor and non-motor symptoms allows for real-time programming of aDBS parameters and assessment of graft performance - creating a feedback loop leading to tailored treatment strategies. Additionally, computational models can simulate the combined effects of neurorestorative and neuromodulatory therapies, optimizing protocols before clinical application [63]. Recently, an emerging treatment approach for complex pathophysiology of PD is a combination of stem cell therapy, adaptive deep brain stimulation (aDBS), and a personalized medicine approach. These individual therapies have their own distinctive therapeutic property and when combined, the patient could have a better clinical outcome since they act on the mechanisms of disease from different angles. While stem cell therapy targets the underlying neuronal loss and allows regrowth of neurons, aDBS allows real-time optimization of neuronal circuit function, and personalized medicine allows for precise targeting of the treatment to the specific characteristics of the individual patient. By applying these modalities together, it is possible to provide treatments at a specific time and in a specific sequence. For instance, aDBS could be applied on the patient population during stem cell transplantation with the objective to stabilise local motor circuits during incorporation of functional connectivity, avoiding symptomatic fluctuations. Personalisation Systems that can be used to select patients who will benefit most from stem cells or NEMS based upon their genomic, biomarker and clinical phenotype [64]. This type of stratification limits variability in response, and maximizes safety and efficacy.

5.1. Stem Cell Therapy and Precision Medicine

In conclusion, stem cell therapy and precision medicine are set to converge and offer a personalized therapeutic solution to the treatment of Parkinson disease (PD). While the ability of cell transplantation to restore lost DA neurons and to afford a neuroprotective effect is very promising, the success of transplantation will depend on the patient's genetic background, on the disease course, and on immune response [65]. Precision medicine will be used to further optimize stem cell-based interventions along these underlying axes for maximal therapeutic efficacy with minimal risk. Genomic profiling facilitates stem cell-based interventions: some disease states and neuronal susceptibility and sensitivity to cell-based therapy have been linked to genetic polymorphisms such as LRRK2, GBA, PINK1 and SNCA. Thus, identification of these genetic determinants may help clinicians recognize the subset of the population which will respond best to transplantation and thus most appropriate targeting of cell types, differentiation protocols, and immunomodulation strategies [66]. For instance, iPSCs identified from patient derived somatic cells may reduce immune rejection significantly compared to adult derived donor stem cells and also offer platform for gene correction of patients with pathogenic mutations for safety and functional integration.

Biomarker profiling is therefore useful for timing and targeting of transplantation. Conclusions: Cerebrospinal fluid a-synuclein, neurofilament light chain (NfL) and inflammation-specific biomarkers provide a clinical approach that may enable graftable time points to be selected when the neuroinflammatory activity is reduced and the neural microenvironment is at an optimal integrative stasis. Neuroimaging (dopamine transporter (DaT) imaging and functional MRI) may be used for very high-resolution localization and measurement of the striatonigral pathway to guide graft delivery and post-transplantation connectivity [67]. Furthermore, predictive and computational platforms to model graft success, at least partly based on patient-specific parameters and data-driven decision-making factors, for graft survival, graft integration and functional outcome prediction are applied. If digital ambulatory technology can help the clinician rapidly see that motor and non-motor posttransplant symptoms are occurring, this allows flexibility to enhance adjunct therapy such as adaptive DBS or pharmaceutical support to continue optimizing care [68]. In conclusion, a combination of stem cell therapy and precision medicine will utilize genomic, biomarker and computational insights to target therapy. This combination leads to greater graft survival, restoration of function, safety, and limits heterogeneity of therapeutic response. This will take regenerative approaches to the next level to attempt to achieve patient-specific disease modifying therapy for PD by adopting a patient-specific approach [69].

5.2. aDBS in Personalized Care

Adaptive deep brain stimulation (aDBS) has emerged as a key component in the field of personalized medicine for Parkinson's disease (PD), and it offers dynamic and real-time neuromodulation based on a patient own individual neural activity [70]. A difference to standard DBS, which provides constant stimulation independently of the dynamic nature of motor symptoms is that aDBS uses closed-loop recording systems detecting neurophysiological biomarkers e.g., subthalamic nucleus (STN) beta-band oscillations to adapt stimulation parameters to the instantaneous motor state of the patient [71]. Personalisation by careful selection of patients, integrating clinical and genetic information with neuroimaging for the most part, patients who have been selected for aDBS have experienced significant motor fluctuations, dyskinesias or poor response to pharmacological therapy. We utilize pre-operative imaging and electrophysiological mapping for accurate electrode localization and target selection for the maximum therapeutic effect to the nuclei.

Once implanted, aDBS devices have the following capabilities:

1. Continuous local field potential (LFP) recording and other biomarkers able to modulate stimulation in real-time.
2. Machine learning algorithms are used to predict motor fluctuations from each of these signals, which then optimise the stimulation pattern to enhance the motor control while limiting stimulation-induced dysarthria, impaired gait, or involuntary movements. This personalised approach also ensures that stimulation amplitudes are as low as possible, which in turn helps to maximise battery life and decrease the frequency with which a device needs to be replaced [72].

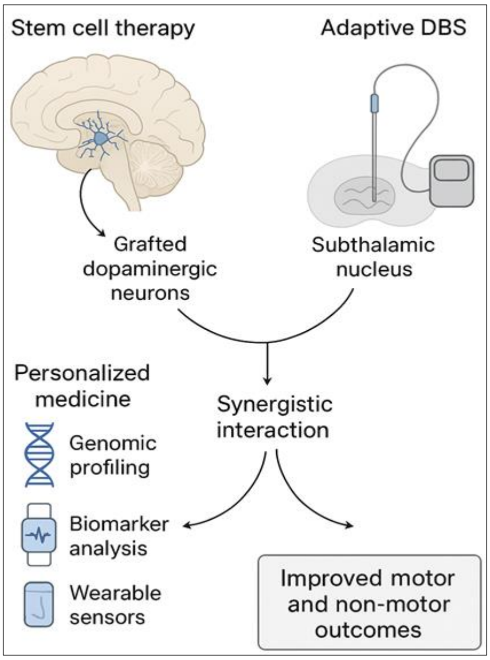

Fig 1: Synergistic Integration of Stem Cell Therapy, Adaptive DBS, and Personalized Medicine in Parkinson's Disease

The integrative approach to digital health takes personalization one step beyond. Remote monitoring systems and wearable sensors provide continuous feedback in tremor frequency, bradykinesia, gait and daily activity. Based on these data, AI-powered analytics can fine-tune aDBS programming, modify therapy based on changes in symptom profile and anticipate clinical deterioration [73]. This enables stimulation that is in tune with that patient's function throughout the disease. Several observational studies have found individual aDBS protocols to be related to improved motor outcomes, when compared with standard DBS, and better quality of life and diminished medication burden [74]. Furthermore, aDBS enables a synergy between aDBS and other therapies as demonstrated within a combined study of aDBS and stem cell transplant in which grafting is stabilized by aDBS. In short, aDBS is a model of precision neuromodulation for PD that relies on near continuous adaptation of stimulation to individual biological and functional properties. Personalised therapy: aDBS optimises efficacy by tailoring therapy to a patient's specific pathophysiology, reduces the incidence of adverse effects and is part of an integrated personalised approach to treating Parkinson disease [75].

6. Future Directions

Although there has been significant progression in the field of Parkinson disease (PD) therapeutics, there are still many knowledge gaps and translational hurdles to overcome. Stem cell therapy, adaptive deep brain stimulation (aDBS), and precision medicine are highly promising new interventions, but confirmatory large-scale and long-term clinical trials are needed to establish safety, efficacy and long-term durability [76]. Optimizing procedures for stem cell differentiation, graft survival and functional integration is still a priority, and identification and validation of reliable biomarkers are essential for precision medicine and aDBS approaches [77]. Combinations of SC transplantation and neuromodulation are actively in ongoing clinical trials designed to improve graft engraftment and functional recovery. More sophisticated imaging and AI-based patient monitoring are increasingly being incorporated into such trials so that patients' individual response can be assessed in real time and therapy can then be iteratively adjusted. In addition, patient-derived induced pluripotent stem cells (iPSCs) open the possibilities of a personalized regenerative therapy, but they are still an expensive method and difficult to scale up [78].

There is a limited understanding of patient response, immune rejection, tumorigenicity and technical issues associated with closed loop DBS systems. Results should be trans centrically reproducible across centres and this requires harmonisation of surgical approach, medical device programming and outcome measures. Of course, the source of stem cell preparation and genetic engineering will need to be continually monitored, as will the regulatory structures to guarantee patient protection and fair access. For now, multimodal approaches are also significant, which are the regenerative therapy combined with neuromodulation and data-driven personalised medicine [79]. As such, it is truly only digital monitoring coupled with an understanding of genomic profiling provided via AI analytics that will enable any intelligent adaptive patient centric intervention to occur [80]. In addition, innovative approaches with new biomarkers, neuroprotective agents, and combinatorial disease modification/slowing of progression are being explored.

Finally, these novel therapies will need to eventually be translated into safe, accessible and clinically effective therapies for treatment of PD. Finally, we can conclude that data derived from stem cell therapy, adaptive DBS and precision medicine will be critical in unlocking the full potential of such technologies and ensuring safe and effective application of these technologies to improving the outcome and quality of life for patients with PD.

7. Conclusion

Parkinson disease (PD) is an enigmatic neurodegenerative condition with considerable motor and non-motor burden, in which there is a need for new therapeutic strategies outside of standard pharmacological and surgical approaches. Stem cell therapy, adaptive deep brain stimulation (aDBS) and personalized medicine are emerging treatment modalities that target different disease aspects and are expected to have additive effects. Stem cell therapy offers the opportunity for neuronal replacement and neuroprotection, which will lead to functional recovery and disease modification. Recent advances in induced pluripotent stem cells (iPSCs) and human embryonic stem cell-derived dopaminergic progenitors have been shown to be feasible, to survive grafting, and to have shown initial improvement of motor function in the earliest clinical trials. Adaptive DBS (ABS) is a technique, which improves neuromodulation by tailoring stimulation to current neurophysiological biomarkers for managing movement and minimizing side effects, and allows for personalized therapy. Personalised medicine combines genomic, biomarker and digital health data for the personalisation of treatments, the optimisation of treatment choice, and the surveillance of disease progression in an individual patient.

The combined use of these approaches enables a comprehensive and patient-targeted therapeutic approach in which neuronal loss, circuit dysfunction, and individual heterogeneity are addressed in parallel. Optimization of therapy with continuous feedback and adaptive adjustment is further developed using digital and Artificial Intelligence-based monitoring. Despite technical challenges, heterogeneity of response to therapy, safety considerations long-term and in individual patients and regulatory aspects, continuous research and clinical developments provide attractive options. Together, these cutting-edge modalities are leading the way to disease modifying precision-guided interventions; radically changing the way we treat Parkinson disease and thereby enhancing the quality of life of all affected individuals.

List Of Abbreviations

PD: Parkinson's Disease; **DBS:** Deep Brain Stimulation; **aDBS**: Adaptive Deep Brain Stimulation; **STN**: Subthalamic Nucleus; **GPi:** Globus Pallidus Internus; **LRRK2**: Leucine-Rich Repeat Kinase 2; **PINK1:** Phosphatase and Tensin Homolog Induced Kinase 1; **SNCA**: Alpha-Synuclein; **GBA**: Glucosylceramidase Beta; **hESCs**: Human Embryonic Stem Cells; **iPSCs:** Induced Pluripotent Stem Cells; **MSCs:** Mesenchymal Stem Cells; **hPSCs**: Human Pluripotent Stem Cells; **BDNF**: Brain-Derived Neurotrophic Factor; **GDNF**: Glial cell line-Derived Neurotrophic Factor; **VEGF**: Vascular Endothelial Growth Factor; **LFPs**: Local Field Potentials; **NfL**: Neurofilament Light chain; **fMRI**: Functional Magnetic Resonance Imaging; **SPECT**: Single Photon Emission Computed Tomography.

Ethical Approval

Not applicable.

Consent for Publication

Not applicable.

Human and Animal Ethical Right

Not applicable.

Conflict of Interest

The authors declared no conflict of interest, and no funding was required to conduct these review data.

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Availability of Data and Materials

The data supporting this study findings will be available in the cited references.

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Author Contribution

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Reference

1. Latif S, Jahangeer M, Razia DM, Ashiq M, Ghaffar A, Akram M, El Allam A, Bouyahya A, Garipova L, Shariati MA, Thiruvengadam M. Dopamine in Parkinson's disease. Clin Chim Acta [Internet]. 2021 Nov 1;522:114-26. Available from: https://doi.org/10.1016/j.cca.2021.08.005
2. Cacabelos R. Parkinson's disease: from pathogenesis to pharmacogenomics. Int J Mol Sci [Internet]. 2017 Mar 4;18(3):551. Available from: https://doi.org/10.3390/ijms18030551
3. Goloborshcheva VV, Kucheryanu VG, Voronina NA, Teterina EV, Ustyugov AA, Morozov SG. Synuclein proteins in MPTP-induced death of Substantia Nigra pars compacta dopaminergic neurons. Biomedicines [Internet]. 2022 Sep 14;10(9):2278. Available from: https://doi.org/10.3390/biomedicines10092278
4. Khan AU, Akram M, Daniyal M, Zainab R. Awareness and current knowledge of Parkinson's disease: a neurodegenerative disorder. Int J Neurosci [Internet]. 2019 Jan 2;129(1):55-93. Available from: https://doi.org/10.1080/00207454.2018.1486837
5. Sarkar S, Raymick J, Imam S. Neuroprotective and therapeutic strategies against Parkinson's disease: recent perspectives. Int J Mol Sci [Internet]. 2016 Jun 8;17(6):904. Available from: https://doi.org/10.3390/ijms17060904
6. Mishra N, Ashique S, Garg A, Rai VK, Dua K, Goyal A, Bhatt S. Role of siRNA-based nanocarriers for the treatment of neurodegenerative diseases. Drug Discov Today [Internet]. 2022 May 1;27(5):1431-40. Available

from: https://doi.org/10.1016/j.drudis.2022.02.004

7. Bloem BR, Okun MS, Klein C. Parkinson’s disease. Lancet [Internet]. 2021 Jun 12;397(10291):2284-303. Available from: https://doi.org/10.1016/S0140-6736(21)00218-X
8. Stocchi F, Bravi D, Emmi A, Antonini A. Parkinson disease therapy: current strategies and future research priorities. Nat Rev Neurol [Internet]. 2024 Dec;20(12):695-707. Available from: https://doi.org/10.1038/s41582-024-01030-0
9. Pal R, Pandey P, Manju, Chawra H. A text book molecular pharmaceutics (nano technology & targeted DDS) (NTDS). [place unknown: publisher unknown]; 2024.
10. Alameer AA, Alhuraysi MA, Alhazmi MI, Al-Ghamdi WA, Alshehri SA, Maashi SM, Al-Ghashmari KH. Parkinson disease: an overview for the management techniques via physical therapy. J Ecohumanism. 2024 Dec 30;3(8):12698-707.
11. Saini L, Dubey A, Pal R, Pandey P, Mandal R. Synthetic and natural polymers enhancing drug delivery and their treatment: a comprehensive review. J Drug Deliv Ther [Internet]. 2024;14(10):153-65. Available from: https://doi.org/10.22270/jddt.v14i10.6802
12. Rees RN, Noyce AJ, Schrag AE. Identification of prodromal Parkinson disease: we may be able to but should we? Neurology [Internet]. 2024 Jun 11;102(11):e209394. Available from: https://doi.org/10.1212/WNL.0000000000209394
13. Zhang J. Mining imaging and clinical data with machine learning approaches for the diagnosis and early detection of Parkinson’s disease. NPJ Parkinsons Dis [Internet]. 2022 Jan 21;8(1):13. Available from: https://doi.org/10.1038/s41531-021-00267-9
14. Mathur S, Mathur S. Patient empowerment for those living with Parkinson’s disease. J Parkinsons Dis [Internet]. 2024 Aug 13;14(s1):S173-80. Available from: https://doi.org/10.3233/JPD-240135
15. Markulin I, Matasin M, Turk VE, Salković-Petrisic M. Challenges of repurposing tetracyclines for the treatment of Alzheimer’s and Parkinson’s disease. J Neural Transm [Internet]. 2022 Jun;129(5):773-804. Available from: https://doi.org/10.1007/s00702-022-02492-0
16. Mandal R. A new era for transforming multidrug-resistant tuberculosis treatment: steps, science, and success - International Conference at Amity University, MP, India [Internet]. 2024. Available from: https://doi.org/10.13140/RG.2.2.10355.64804
17. Nguyen PA, Nguyen TD, Park S. Advanced gene therapy in Parkinson’s disease through innovations in drug delivery systems. J Pharm Investig [Internet]. 2025 Apr 22;55:1-29. Available from: https://doi.org/10.1007/s40005-025-00664-5
18. Ibarra-Ramírez E, Montes M, Urrutia RA, Reginensi D, Segura González EA, Estrada-Petrocelli L, Gutierrez-Vega A, Appaji A, Molino J. Metallic nanoparticles applications in neurological disorders: a review. Int J Biomater [Internet]. 2025;2025(1):4557622. Available from: https://doi.org/10.1155/2025/4557622
19. Pal R, Pandey P, Chawra H, Khan Z. Nano drug delivery carriers (nanocarriers): a promising targeted strategy in tuberculosis and pain treatment. Pharm Nanotechnol [Internet]. 2025;13. Available from: https://doi.org/10.2174/0122117385367493250224103839
20. Li T, Zou S, Zhang Z, Liu M, Liang Z. Efficacy of pramipexole on quality of life in patients with Parkinson’s disease: a systematic review and meta-analysis. BMC Neurol [Internet]. 2022 Aug 25;22(1):320. Available from: https://doi.org/10.1186/s12883-022-02837-5
21. Pal R, Pandey P, Chawra H, Singh R. Niosomal as potential vesicular drug nano-carriers for the treatment of tuberculosis (TB). Nanosci Nanotechnol Asia [Internet]. 2024;14. Available from: https://doi.org/10.2174/0122106812323829240919050438
22. Wolff A, Schumacher NU, Pürner D, Machetanz G, Demleitner AF, Feneberg E, Hagemeier M, Lingor P. Parkinson’s disease therapy: what lies ahead? J Neural Transm [Internet]. 2023 Jun;130(6):793-820. Available from: https://doi.org/10.1007/s00702-023-02627-x
23. Colella P. Advances in pompe disease treatment: from enzyme replacement to gene therapy. Mol Diagn Ther [Internet]. 2024 Nov;28(6):703-19. Available from: https://doi.org/10.1007/s40291-024-00734-7
24. Krellman JW, Mercuri G. Cognitive interventions for neurodegenerative disease. Curr Neurol Neurosci Rep [Internet]. 2023 Sep;23(9):461-8. Available from: https://doi.org/10.1007/s11910-023-01293-9
25. Mansour A, Eldin MH, El-Sherbiny I. Metallic nanomaterials in Parkinson’s disease: a transformative approach for early detection and targeted therapy. J Mater Chem B [Internet]. 2025. Available from: https://doi.org/10.1039/D4TB01736A
26. Andrade S, Nunes D, Dabur M, Ramalho MJ, Pereira MC, Loureiro JA. Therapeutic potential of natural compounds in neurodegenerative diseases: insights from clinical trials. Pharmaceutics [Internet]. 2023 Jan 7;15(1):212. Available from: https://doi.org/10.3390/pharmaceutics15010212
27. Ruggiero M, Calvello R, Porro C, Messina G, Cianciulli A, Panaro MA. Neurodegenerative diseases: can caffeine be a powerful ally to weaken neuroinflammation? Int J Mol Sci [Internet]. 2022 Oct 26;23(21):12958. Available from: https://doi.org/10.3390/ijms232112958
28. Kang E, Friz D, Lipsey K, Foster ER. Empowerment in people with Parkinson’s disease: a scoping review and qualitative interview study. Patient Educ Couns [Internet]. 2022 Oct 1;105(10):3123-33. Available from: https://doi.org/10.1016/j.pec.2022.06.006
29. Padilla-Godínez FJ, Ruiz-Ortega LI, Guerra-Crespo M. Nanomedicine in the face of Parkinson’s disease: from drug delivery systems to nanozymes. Cells [Internet]. 2022 Oct 31;11(21):3445. Available from: https://doi.org/10.3390/cells11213445
30. Dunning EE, Decourt B, Zawia NH, Shill HA, Sabbagh MN. Pharmacotherapies for the treatment of progressive supranuclear palsy: a narrative review. Neurol Ther [Internet]. 2024 Aug;13(4):975-1013. Available from: https://doi.org/10.1007/s40120-024-00636-4
31. Markiewicz M, Madetko-Alster N, Alster P. Quality of life in patients with progressive supranuclear palsy: a review of literature and implications for practice. Front Neurol [Internet]. 2024 Nov 20;15:1476488. Available from: https://doi.org/10.3389/fneur.2024.1476488
32. Lau K, Kotzur R, Richter F. Blood–brain barrier alterations and their impact on Parkinson’s disease

pathogenesis and therapy. Transl Neurodegener [Internet]. 2024 Jul 29;13(1):37. Available from: https://doi.org/10.1186/s40035-024-00424-9

33. Markos S, Galibov M. Rehabilitation of women with neurodegenerative diseases. Phys Med Rehabil Clin N Am [Internet]. 2025 May 1;36(2):389-98. Available from: https://doi.org/10.1016/j.pmr.2024.11.002
34. Ebrahimi P, Davoudi E, Sadeghian R, Zadeh AZ, Razmi E, Heidari R, Morowvat MH, Sadeghian I. *In vivo* and ex vivo gene therapy for neurodegenerative diseases: a promise for disease modification. Naunyn Schmiedebergs Arch Pharmacol [Internet]. 2024 Oct;397(10):7501-30. Available from: https://doi.org/10.1007/s00210-024-03146-8
35. Clausen L, Okarmus J, Voutsinos V, Meyer M, Lindorff-Larsen K, Hartmann-Petersen R. PRKN-linked familial Parkinson's disease: cellular and molecular mechanisms of disease-linked variants. Cell Mol Life Sci [Internet]. 2024 Dec;81(1):223. Available from: https://doi.org/10.1007/s00018-024-05263-0
36. Franco GA, Interdonato L, Cordaro M, Cuzzocrea S, Di Paola R. Bioactive compounds of the Mediterranean diet as nutritional support to fight neurodegenerative disease. Int J Mol Sci [Internet]. 2023 Apr 15;24(8):7318. Available from: https://doi.org/10.3390/ijms24087318
37. Stecca C, Abdeljalil O, Sridhar SS. Metastatic urothelial cancer: a rapidly changing treatment landscape. Ther Adv Med Oncol [Internet]. 2021 Sep;13:17588359211047352. Available from: https://doi.org/10.1177/17588359211047352
38. Mandal R. Nano spectroscopic device for T.B detection (U.K. design patent). [place unknown: publisher unknown]; 2025.
39. Agostini F, Masato A, Bubacco L, Bisaglia M. Metformin repurposing for Parkinson disease therapy: opportunities and challenges. Int J Mol Sci [Internet]. 2021 Dec 30;23(1):398. Available from: https://doi.org/10.3390/ijms23010398
40. Hanna L, Poluyi E, Ikwuegbuenyi C, Morgan E, Imaguezegie G. Peripheral inflammation and neurodegeneration; a potential for therapeutic intervention in Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Egypt J Neurosurg [Internet]. 2022 May 9;37(1):15. Available from: https://doi.org/10.1186/s41984-022-00160-3
41. Zhao W, Shao X, Wang Z, Mi C, Wang Y, Qi X, Ding X. Deep brain stimulation for Parkinson's disease: bibliometric analysis of the top 100 cited literature. Front Aging Neurosci [Internet]. 2024 Oct 16;16:1413074. Available from: https://doi.org/10.3389/fnagi.2024.1413074
42. Pal R, Mandal R, Dubey A, Saini P. Recent advances in transdermal drug delivery systems: review article. J Pharma Insights Res [Internet]. 2024;2:87-97. Available from: https://doi.org/10.69613/p3cspw10
43. Gaztanaga W. Palliative care for Parkinson's disease: literature review. [place unknown: publisher unknown]; [date unknown].
44. Santiago JA, Potashkin JA. Physical activity and lifestyle modifications in the treatment of neurodegenerative diseases. Front Aging Neurosci [Internet]. 2023 May 26;15:1185671. Available from: https://doi.org/10.3389/fnagi.2023.1185671
45. Dalakas MC. Stiff-person syndrome and related disorders—diagnosis, mechanisms and therapies. Nat Rev Neurol [Internet]. 2024 Oct;20(10):587-601. Available from: https://doi.org/10.1038/s41582-024-01023-z
46. Nayab DE, Din FU, Ali H, Kausar WA, Urooj S, Zafar M, Khan I, Shabbir K, Khan GM. Nano biomaterials based strategies for enhanced brain targeting in the treatment of neurodegenerative diseases: an up-to-date perspective. J Nanobiotechnology [Internet]. 2023 Dec 13;21(1):477. Available from: https://doi.org/10.1186/s12951-023-02209-1
47. Yesmin S, Kombo HZ, Singh L, Singh G. Experimental models and behavioral parameters for evaluation of Parkinson disease. In: AIP Conference Proceedings [Internet]. 2025 Jul 10;2807(1):040007. Available from: https://doi.org/10.1063/5.0225128
48. Toader C, Tataru CP, Munteanu O, Serban M, Covache-Busuioc RA, Ciurea AV, Enyedi M. Decoding neurodegeneration: a review of molecular mechanisms and therapeutic advances in Alzheimer's, Parkinson's, and ALS. Int J Mol Sci [Internet]. 2024 Nov 24;25(23):12613. Available from: https://doi.org/10.3390/ijms252312613
49. Rai SN, Tiwari N, Singh P, Mishra D, Singh AK, Hooshmandi E, Vamanu E, Singh MP. Therapeutic potential of vital transcription factors in Alzheimer's and Parkinson's disease with particular emphasis on transcription factor EB mediated autophagy. Front Neurosci [Internet]. 2021 Dec 14;15:777347. Available from: https://doi.org/10.3389/fnins.2021.777347
50. Mandal R, Pal R. Emerging technologies in tuberculosis diagnosis: a comprehensive review. Int J Pharm Res Dev [Internet]. 2025;7:265-77. Available from: https://doi.org/10.33545/26646862.2025.v7.i1d.119
51. Cheslow L, Snook AE, Waldman SA. Biomarkers for managing neurodegenerative diseases. Biomolecules [Internet]. 2024 Mar 26;14(4):398. Available from: https://doi.org/10.3390/biom14040398
52. Akbar A, Haider R, Agnello L, Noor B, Maqsood N, Atif F, Ali W, Ciaccio M, Tariq H. CRISPR in neurodegenerative diseases treatment: an alternative approach to current therapies. Genes [Internet]. 2025 Jul 22;16(8):850. Available from: https://doi.org/10.3390/genes16080850
53. Benameur T, Giacomucci G, Panaro MA, Ruggiero M, Trotta T, Monda V, Pizzolorusso I, Lofrumento DD, Porro C, Messina G. New promising therapeutic avenues of curcumin in brain diseases. Molecules [Internet]. 2022 Jan;27(1):236. Available from: https://doi.org/10.3390/molecules27010236
54. Calderone A, Latella D, La Fauci E, Puleo R, Sergi A, De Francesco M, Mauro M, Foti A, Salemi L, Calabrò RS. Artificial intelligence-driven neuromodulation in neurodegenerative disease: precision in chaos, learning in loss. Biomedicines [Internet]. 2025 Aug 30;13(9):2118. Available from: https://doi.org/10.3390/biomedicines13092118
55. Chaurasia S, Dogra SS, Hussain MS, Kumar R, Khurana N. Novel pharmaceutical interventions for drug targeting in Parkinson's disease. Curr Drug Ther [Internet]. 2024 Oct 17. Available from: https://doi.org/10.2174/011574885519666240226094632
56. Tan QY, Cox NJ, Lim SE, Coutts L, Fraser SD, Roberts

HC, Ibrahim K. The experiences of treatment burden in people with Parkinson's disease and their caregivers: a systematic review of qualitative studies. J Parkinsons Dis [Internet]. 2021 Oct 12;11(4):1597-617. Available from: https://doi.org/10.3233/JPD-212623

57. Siafaka PI, Okur ME, Erim PD, Çağlar EŞ, Özgenç E, Gündoğdu E, Köprülü RE, Karantas ID, Üstündağ Okur N. Protein and gene delivery systems for neurodegenerative disorders: where do we stand today? Pharmaceutics [Internet]. 2022 Nov 10;14(11):2425. Available from: https://doi.org/10.3390/pharmaceutics14112425
58. Farzan M, Abedi B, Bhia I, Madanipour A, Farzan M, Bhia M, Aghaei A, Kheirollahi I, Motallebi M, Amini-Khoei H, Ertas YN. Pharmacological activities and molecular mechanisms of sinapic acid in neurological disorders. ACS Chem Neurosci [Internet]. 2024 Jul 31;15(16):2966-81. Available from: https://doi.org/10.1021/acschemneuro.4c00218
59. Nehra A, Makkar R, Singh RK, Rajan R, Khan MA, Srivastava AK. Is disease a threat to identity? A systematic review of Parkinson's disease and personal identity. Indian J Public Health [Internet]. 2023 Jan 1;67(1):117-22. Available from: https://doi.org/10.4103/ijph.ijph_1650_22
60. Chakrabarti S, Bisaglia M. Oxidative stress and neuroinflammation in Parkinson's disease: the role of dopamine oxidation products. Antioxidants [Internet]. 2023 Apr 18;12(4):955. Available from: https://doi.org/10.3390/antiox12040955
61. Park TY, Jeon J, Cha Y, Kim KS. Past, present, and future of cell replacement therapy for Parkinson's disease: a novel emphasis on host immune responses. Cell Res [Internet]. 2024 Jul;34(7):479-92. Available from: https://doi.org/10.1038/s41422-024-00962-8
62. Mandal R, Saini P, Pal R, Pandey P, Dubey A. Coating tablets, compositions, recent advancement and current status: a comprehensive review. J Drug Deliv Ther [Internet]. 2024;14:182-95. Available from: https://doi.org/10.22270/jddt.v14i10.6809
63. Alkahtani S, Al-Johani NS, Alarifi S. Mechanistic insights, treatment paradigms, and clinical progress in neurological disorders: current and future prospects. Int J Mol Sci [Internet]. 2023 Jan 10;24(2):1340. Available from: https://doi.org/10.3390/ijms24021340
64. Wang Z, Song B, Liu C, Ma H, Bai Z, Carneiro MA, Youssef L, Chen C, Zhang L, Wang D, Wang D. Effects of boxing exercise in people with Parkinson's disease: a systematic review. Front Aging Neurosci [Internet]. 2025 Mar 27;17:1505326. Available from: https://doi.org/10.3389/fnagi.2025.1505326
65. De Miranda BR, Goldman SM, Miller GW, Greenamyre JT, Dorsey ER. Preventing Parkinson's disease: an environmental agenda. J Parkinsons Dis [Internet]. 2022 Jan 21;12(1):45-68. Available from: https://doi.org/10.3233/JPD-212922
66. Shan C, Zhang C, Zhang C. The role of IL-6 in neurodegenerative disorders. Neurochem Res [Internet]. 2024 Apr;49(4):834-46. Available from: https://doi.org/10.1007/s11064-023-04093-3
67. Duan L, Li X, Ji R, Hao Z, Kong M, Wen X, Guan F, Ma S. Nanoparticle-based drug delivery systems: an inspiring therapeutic strategy for neurodegenerative diseases. Polymers [Internet]. 2023 May 5;15(9):2196. Available from: https://doi.org/10.3390/polym15092196
68. Abijo A, Lee CY, Huang CY, Ho PC, Tsai KJ. The beneficial role of photobiomodulation in neurodegenerative diseases. Biomedicines [Internet]. 2023 Jun 26;11(7):1828. Available from: https://doi.org/10.3390/biomedicines11071828
69. Waris A, Ali A, Khan AU, Asim M, Zamel D, Fatima K, Raziq A, Khan MA, Akbar N, Baset A, Abourehab MA. Applications of various types of nanomaterials for the treatment of neurological disorders. Nanomaterials [Internet]. 2022 Jun 22;12(13):2140. Available from: https://doi.org/10.3390/nano12132140
70. Garon M, Weck C, Leta V, Dijkstra BW, Muente C, Gentile G, Trivedi D, Groot MM, Lorenzl S, Odin P, Konitsiotis S. Early thinking palliative care for people with Parkinson's disease: a thematic synthesis based on a systematic mixed-methods review. J Parkinsons Dis [Internet]. 2025 Jun;15(4):710-58. Available from: https://doi.org/10.3233/JPD-245360
71. Goncalves PB, Sodero AC, Cordeiro Y. Green tea epigallocatechin-3-gallate (EGCG) targeting protein misfolding in drug discovery for neurodegenerative diseases. Biomolecules [Internet]. 2021 May 20;11(5):767. Available from: https://doi.org/10.3390/biom11050767
72. Ko TK, Tan DJ. Is disrupted mitophagy a central player to Parkinson's disease pathology? Cureus [Internet]. 2023 Feb 25;15(2):e35458. Available from: https://doi.org/10.7759/cureus.35458
73. Ahmady H, Afrand M, Motaqi M, Meftahi GH. Utilizing Sertoli cell transplantation as a therapeutic technique for the management of neurodegenerative diseases. Arch Razi Inst [Internet]. 2024 Aug 1;79(4):701. Available from: https://doi.org/10.32592/ARI.2024.79.4.701
74. Abd Rashed A, Abd Rahman AZ, Rathi DN. Essential oils as a potential neuroprotective remedy for age-related neurodegenerative diseases: a review. Molecules [Internet]. 2021 Feb 19;26(4):1107. Available from: https://doi.org/10.3390/molecules26041107
75. Yi LX, Tan EK, Zhou ZD. The α-synuclein seeding amplification assay for Parkinson's disease. Int J Mol Sci [Internet]. 2025 Jan 4;26(1):389. Available from: https://doi.org/10.3390/ijms26010389
76. Omar SS, Ali RH, Abdullah SH, Hussein DM, Radha BM, Latif AB, Ali SM, Hiwa DS, Ahmed HK, Hamasaeed AG, Othman S. Role of durvalumab (anti-PD-L1) in the management of mesothelioma: a systematic review of the current literature. Barw Med J [Internet]. 2023 Dec 5. Available from: https://doi.org/10.5847/bmj.2023.003
77. Kiran P, Debnath SK, Neekhra S, Pawar V, Khan A, Dias F, Pallod S, Srivastava R. Designing nanoformulation for the nose-to-brain delivery in Parkinson's disease: advancements and barrier. Wiley Interdiscip Rev Nanomed Nanobiotechnol [Internet]. 2022 Jan;14(1):e1768. Available from: https://doi.org/10.1002/wnan.1768
78. Zhang LP, Liao JX, Liu YY, Luo HL, Zhang WJ. Potential therapeutic effect of olfactory ensheathing cells in neurological diseases: neurodegenerative diseases and peripheral nerve injuries. Front Immunol [Internet]. 2023 Oct 17;14:1280186. Available from: https://doi.org/10.3389/fimmu.2023.1280186
79. Magaña JC, Deus CM, Giné-Garriga M, Montane J,

Pereira SP. Exercise-boosted mitochondrial remodeling in Parkinson’s disease. Biomedicines [Internet]. 2022 Dec 12;10(12):3228. Available from: https://doi.org/10.3390/biomedicines10123228

80. Quan Y, Xu J, Xu Q, Guo Z, Ou R, Shang H, Wei Q. Association between the risk and severity of Parkinson’s disease and plasma homocysteine, vitamin B12 and folate levels: a systematic review and meta-analysis. Front Aging Neurosci [Internet]. 2023 Oct 26;15:1259531. Available from: https://doi.org/10.3389/fnagi.2023.1259531