Published in final edited form as:

Nat Rev Neurol. 2019 April ; 15(4): 204–223. doi:10.1038/s41582-019-0155-7.

Emerging therapies in Parkinson disease — repurposed drugs and new approaches

Ahmad Elkouzi[1,3,*], **Vinata Vedam-Mai**[1,2,3], **Robert S. Eisinger**[1], **Michael S. Okun**[1,2]

[1]Department of Neurology, Fixel Institute for Neurological Diseases, University of Florida, Gainesville, FL, USA.

[2]Department of Neurosurgery, Fixel Institute for Neurological Diseases, University of Florida, Gainesville, FL, USA.

[3]These authors contributed equally: Ahmad Elkouzi, Vinata Vedam-Mai

Since the publication of *An Essay on the Shaking Palsy* by James Parkinson two centuries ago, our understanding of the genetics, pathogenesis and clinical heterogeneity of Parkinson disease (PD) has evolved substantially. PD involves more than degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNc), and its manifestations are recognizable beyond the car- dinal motor features of tremor, rigidity, bradykinesia and postural instability.

A complex interplay between genes and the environ- ment shapes the development of PD[1], and the existence of multiple pathways involving genes, proteins, cellular organelles and neural networks could contribute to the heterogeneity of symptom manifestation. Individual pathogenic pathways have been targeted for sympto- matic improvement and disease modification with var- iable success. Although dopaminergic therapies remain the gold standard for symptomatic management of PD, several unmet needs remain regarding treatment of dopaminergic-resistant motor and nonmotor symp- toms and for interventions that modify the natural clinical course of the disease. Many pharmacological agents specifically designed for disease modification have failed to meet the primary end point in multiple clinical trials over the past several decades. Challenges in these studies included, but were not limited to, the clinical heterogeneity of the population, patient selec- tion (for example, inclusion of patients with concurrent other neurodegenerative or vascular disease that might influence the outcome of the drug studied), lack of an adequate preclinical model

* ahmad.elkouzi@neurology.ufl.edu.

Author contributions

All authors researched data for the article, wrote the article and reviewed the manuscript before submission. A.E., V.V.-M. and M.S.O. made a substantial contribution to discussion of article content.

Competing interests

V.V.-M. is supported by a grant for the deep brain stimulation brain bank from Abbott. M.S.O. serves as a consultant for the Parkinson's Foundation and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, the Smallwood Foundation, the Bachmann–Strauss Foundation, the Tourette Syndrome Association and the UF Foundation. M.S.O. has previously received honoraria but in the past >60 months has received no support from industry. M.S.O. has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients and Cambridge (movement disorder books). M.S.O. is an associate editor for the *New England Journal of Medicine: Journal Watch Neurology*. M.S.O. has participated in continuing medical edu- cation and educational activities on movement disorders (in the past 36 months) sponsored by PeerView, Prime, QuantiaMD, WebMD, Medicus, MedNet, Henry Stewart and Vanderbilt University. M.S.O. has participated as a site principal investi- gator (PI) and/or co-PI for several NIH, foundation and industry- sponsored trials over the years but has not received honoraria. A.E. and R.S.E. have no competing interests.

of sporadic PD, lack of a disease biomarker and failure to identify preclinical PD. Another major challenge has been identification of the ideal time frame to apply disease-modifying thera- pies[2]. The heterogeneity of PD has led to its classifica- tion into clinical subtypes[3,4] that reflect biological and pathophysiological differences among individuals with PD[4]. These differences suggest that individualization and precision treatment might be necessary to achieve disease modification.

In this Review, we discuss the emerging non- dopaminergic therapies for PD with a focus on dis- ease modification and treatment of motor symptoms. We examine pharmacological approaches, including small-molecule inhibitors, calcium channel blockers, iron chelators, anti-inflammatories and immunother- apies. We provide a summary of the success of these approaches in animal models, which have led to human clinical trials. We also examine non-pharmacological approaches, including gene therapies, neurotrophic fac- tors, cell restoration therapies and electrical modulation of neural circuits with deep brain stimulation (DBS). Although we recognize the important unmet needs in the treatment of nonmotor symptoms for PD, they are beyond the scope of this Review and have been covered extensively elsewhere[5–7].

Disease-modifying pharmacotherapies

Agents for specific molecular pathways

A mutation in *SNCA*, the gene encoding α-synuclein, was the first to be described in hereditary PD[8]. Since this seminal description, many other genetic muta- tions have been attributed to PD, including mutations in *LRRK2* (encoding leucine-rich repeat kinase 2) and *PRKN* (encoding parkin) the most common auto- somal dominant and recessive mutations, respectively. Advances in understanding the genetic pathways in hereditary forms of PD have driven the development of potential disease-modifying therapies, which have been designed to target genes and/or proteins specific to α-synuclein pathology or other PD-related pathways (such as LRRK2-related pathways). Table 1 summarizes common genetic forms of PD, mechanisms of pathology and the latest advances in targeted therapies as reflected by either active clinical trials or drugs in the pipeline. Dysfunction in a single pathway identified by genetic studies might affect other pathways and involve mul- tiple cellular organelles. Targeting multiple pathways simultaneously might therefore be necessary to achieve disease modification.

α-Synuclein.—Friedrich Heinrich Lewy first described intracytoplasmic inclusions in the brains of patients with PD in 1912. This pathological hallmark was later named a ‘Lewy body’ and is formed by abnormal fibril- lary aggregations of α-synuclein protein[9]. α-Synuclein is a natively unfolded, 140-amino-acid protein that has been postulated to modulate synaptic activity and intracellular trafficking[10]. The exact physiological role of the protein is yet to be fully determined. α-Synuclein transitions between different conformations, including native monomers, tetramers and potentially toxic oli- gomers and fibrils[11]. These conformations hypothetically coexist in a dynamic equilibrium governed by factors that accelerate and inhibit fibrillation, such as genetic mutations[12,13]. Toxic α-synuclein oligomers impair deg- radation pathways[14,15], affect mitochondrial function[16,17],

influence endoplasmic reticulum (ER) trafficking[17] and loosen the association between ER and mitochondria, which might disrupt calcium homeostasis between the organelles[18]. Comprehension of the structure, genetics, pathology and spread of α-synuclein has revolutionized targeted therapies for PD.

Reduction of α-synuclein burden can be achieved by two means: reducing its synthesis or increasing its clearance (Table 2). With regards to reduction of syn- thesis, silencing of *SNCA* using small hairpin RNA and antisense oligonucleotides has provided mixed results in preclinical studies and, as a result, these approaches have not yet been explored in clinical trials[12,19]. The major concern is that these silencing approaches might disrupt the as-yet unknown physiological role of the protein. Moreover, the degree of knockdown needed for a ther- apeutic benefit remains unknown. One report showed that β2-adrenergic receptors regulate *SNCA* expression and therefore β2-adrenergic receptor agonists have potential for disease modification by reducing *SNCA* expression and by promoting the health of dopaminer- gic neurons[20]. However, in a large epidemiological study, β2-adrenergic receptor agonists and antagonists were not consistently associated with increased or decreased risk of PD[21]. Further animal and human studies are needed to fully comprehend the effect of β2-adrenergic receptors on PD risk.

Regarding clearance strategies, α-synuclein is degraded both by the ubiquitin–proteasome system and by the autophagy–lysosomal pathway[14,22]. Increasing clearance of α-synuclein via enhancement of protea- somal activity has been studied using small molecules including IU1, a small-molecule inhibitor of USP14 (a proteasome-associated deubiquitinase) with potential for PD treatment[23]. Successful neuroprotection has also been reported following an increase in autophagy in both in vitro and in vivo models of PD[24]. Overexpression of transcription factors such as transcription factor EB (TFEB), lysosome-associated membrane receptor pro- tein 2a (LAMP2a) or beclin 1, regulators of autophagy pathways, might have neuroprotective effects[25–27]. The mTOR pathway has been implicated in the pathogenesis of PD, and small FDA-approved molecules such as rapa- mycin (an mTOR inhibitor) have been shown to protect against neuronal death in animal models of PD[28] and could be used in future clinical trials. These molecules remain at the preclinical stage, and the safety of such compounds for long-term use in patients with PD needs to be thoroughly investigated before any translation into clinical trials.

Inhibition of the misfolding and/or aggregation of α-synuclein has been an appealing approach for disease modification. Several compounds are being tested in clinical trials and are summarized in Table 2. Tyrosine-protein kinase ABL is activated in the brains of patients with PD and in mouse models of PD gen- erated via administration of the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). ABL activation leads to inhibition of parkin through tyros- ine phosphorylation and results in neural degeneration from accumulation of toxic parkin substrates (such as parkin-interacting substrate (PARIS))[29]. Nilotinib is an FDA-approved ABL inhibitor for the treatment of chronic myelogenous leukaemia. Evidence from an MPTP animal model of PD suggests that nilotinib protects dopaminergic neurons[29]. An initial pilot study involving 12 patients with PD showed safety and toler- ability of nilotinib, with good CNS penetration and tar- get engagement[30]. A multicentre phase II double-blind placebo randomized controlled trial (RCT) is under- way to evaluate

the safety and tolerability of nilotinib in PD (NILO-PD). The study will enrol 135 patients and the primary outcome will be safety and tolera- bility of the drug. The secondary outcome will assess motor and cognitive effects of nilotinib on patients with PD[31].

Screening of drug compound libraries has led to the suggestion that some small-molecule inhibitors of protein aggregation are promising drug candidates[32,33] (Table 2). For example, squalamine, a naturally occurring compound, has been shown to inhibit the aggregation and reduce the toxicity of α-synuclein oligomers in neu- rons and in animal models of PD[34]. Another molecule, CLR01, prevents α-synuclein fibrillation by binding to exposed lysine residues. CLR01 was able to ameliorate motor deficits in a mouse model of PD[35]. Encouraging results from preclinical studies with such inhibitors have demonstrated that a better understanding of α-synuclein aggregates could open up new avenues for therapeutic development.

The hypothesis that misfolded α-synuclein spreads by a prion-like mechanism emerged from observed similarities between α-synuclein and classic prion pro- tein structure[19]. α-Synuclein fibrils are known to induce pathology in animal models, resulting in synaptic dys- function and neuronal death[36–39]. Further support of this hypothesis came after the discovery of Lewy body inclusions in grafted embryonic mesencephalic cells years after implantation in brains of patients with PD[37]. Immunization against α-synuclein hypothetically could neutralize the extracellular protein and prevent trans- mission of toxic fibrils. Lymphocyte-activation gene 3 (LAG3) also has been identified as a receptor (and a potential therapeutic target) that could facilitate cell- to-cell transmission of toxic α-synuclein fibrils[40] (fig. 1; Table 2).

An exciting new approach to target oligomeric α-synuclein is the use of antibodies. This approach has been attempted in Alzheimer disease but is new to PD. Several studies have reported neuroprotection after either passive (using an antibody-based approach) or active (using full-length protein or short peptides) immunization in preclinical models[41–44]. Success from these studies has prompted several clinical trials. A phase I clinical trial using PRX002, a monoclonal antibody against α-synuclein, reported that the treatment was safe and tolerable and demonstrated antibody binding to peripheral α-synuclein and cerebrospinal fluid (CSF) penetration[45]. A phase II clinical study is in progress (Table 2). The development of engineered intrabodies (antibodies adapted for intracellular localization) and conformational antibodies could also be ways to target oligomeric α-synuclein. Affitope PD01 and PD03 are active immunotherapies that use a synthetically pro- duced α-synuclein-mimicking peptide. Both agents were shown to be safe and tolerable in initial pilot studies[46]. The SYMPATH consortium, a European collaborative effort, was launched to further enhance the clinical development of α-synuclein vaccines.

α-Synuclein remains the most compelling target for disease modification in PD, but several questions need to be answered before further progress is made. Despite successful disease modification via targeting of α-synuclein in an animal model of PD[11], α-synuclein tox- icity and the potential for disease modification remain to be proved in sporadic PD. Furthermore, the absence of α-synuclein on autopsy in a subset of patients clini- cally diagnosed with PD (such as individuals with PD related to parkin or LRRK2 (refs[1,47,48])) and the presence of α-

synuclein in the brains of people with multiple sys- tem atrophy, Lewy body dementia or lysosomal storage disease[49], and in healthy elderly patients[50], have raised concerns about the specificity of targeting misfolded α-synuclein protein in PD. Patient selection, lack of biomarkers for target engagement and safety and toler- ability of the targeted therapies against α-synuclein have all been major challenges that will need to be overcome in order to achieve successful disease modification.

LRRK2.—LRRK2 is a member of the Ras-of-complex (ROC) family of proteins[51]. Genome-wide association studies (GWAS) and a meta-analysis of GWAS have strengthened the evidence for a link between increased LRRK2 kinase activity and PD[52–54]. The LRRK2 Gly2019Ser mutation, which localizes to the kinase domain of the protein, is the most frequent mutational cause of late-onset PD. Mutations in the GTPase domain of LRRK2 increase kinase activity and can induce par- kinsonism. How LRRK2 mutations cause PD remains unknown, but the mutations seem to impair autophagy and lysosomal function and induce mitochondrial dysfunction[55,56]. The interplay between LRRK2 and α-synuclein is an area of growing research. A functional interaction between LRRK2 and α-synuclein has been proposed and has opened the possibility that LRRK2- targeted therapies could be beneficial for patients with idiopathic PD[57]. The mechanism of this interaction is not fully clear, and new evidence suggests that LRRK2 activ- ity has a minimal effect on the burden of α-synuclein pathology in neurons, indicating that LRRK2 leads to pathogenesis via a different mechanism than α-synuclein[58]. Additional studies will be needed to deter- mine the clinical and therapeutic implications of any interaction between LRRK2 and α-synuclein. Patients with parkinsonism caused by the LRRK2 Gly2019Ser mutation are phenotypically similar to patients with idiopathic PD but have a higher propensity to develop tremor and dystonia and have a slower disease pro- gression than patients with idiopathic PD[59]. LRRK2 interacts with several key proteins associated with PD, which makes it an attractive therapeutic target[60].

Preclinical development and testing of small-molecule inhibitors has shown promise in animal models includ- ing non-human primates. DNL201, a small-molecule LRRK2 inhibitor, achieved 90% inhibition of LRRK2 kinase activity at peak drug blood levels in a phase I study of healthy volunteers. Testing of DNL151, another LRRK2 inhibitor, is in progress in a phase I trial. LRRK2 is highly expressed in kidneys, lungs and the immune system, and several animal studies that have manipulated LRRK2 at the gene or protein level have reported adverse effects, particularly in these systems. LRRK2-knockout mice show structural changes in the renal tubules of the cortex and medulla, but their renal function remains normal. These structural changes did not seem to occur in the context of pharmacological inhibition of LRRK2 (refs[61,62]). In non-human primates, LRRK2 kinase inhi- bition induced morphological changes in the lungs, consisting of an increased size and number of lamellar bodies in type II pneumocytes, raising a potential safety issue in humans[63]. The Michael J. Fox Foundation has initiated an LRRK2 safety initiative to address these concerns, and LRRK2 kinase inhibitors are proceeding towards clinical trials.

The main challenges facing the development of LRRK2-targeted therapies have been the absence of preclinical models to accurately reflect LRRK2-induced PD and the absence of reliable biomarkers for disease progression. Resolution of these issues will be impor- tant to

address safety concerns and to confirm target engagement[64]. New research has suggested a poten- tial role of wild-type LRRK2 kinase activity in idio- pathic PD pathogenesis[65]. The hope is that therapies targeted against LRRK2 might be useful in treating idiopathic PD.

Glucocerebrosidase.—Although homozygous mutation of *GBA* (encoding glucocerebrosidase) results in Gaucher disease, people with heterozygous *GBA* mutations have an increased risk of parkinsonism or dementia[66], and a large multicentre analysis confirmed that the *GBA* muta- tion is a risk factor for PD[67]. Low GBA enzymatic activ- ity has also been implicated in disease acceleration and worsened prognosis in PD[68]. *GBA*-linked parkinsonism is associated strongly with impairment of the α-synuclein lysosomal degradation process. Conversely, increased levels of toxic soluble oligomers are associated with a depletion of lysosomal GBA. These findings are thought to indicate a neurotoxic cycle in patients with *GBA* muta- tion[69,70]. Therapeutically increasing GBA activity might therefore enhance α-synuclein degradation in neurons[70]. Small-molecule chaperones for GBA are being developed for the treatment of Gaucher disease under the premise that the mutant protein is trapped in the ER and that trafficking of the protein to the lysosome will decrease ER-associated degradation and increase lysosomal func- tion[71,72]. Treatment with the GBA chaperone ambroxol in cell culture and subsequently in patients with *GBA* mutation demonstrated that increasing GBA activity pre- sents a feasible therapeutic approach[73]. A clinical trial of ambroxol in PD (AiM-PD) is currently in progress (Table 1). Another chaperone, LTI-291, is also currently undergoing testing for GBA-associated PD. A next- generation small-molecule GBA chaperone, AT3375, is also under development for both Gaucher disease and PD.

Glucosylceramide synthase inhibitors reduce the levels of glucosylceramide and glucosylsphingosine and have been shown to reverse cognitive impairment and decrease α-synuclein aggregation in a GBA mouse model of PD[74]. A phase II clinical trial (MOVES-PD) is underway to test a glucosylceramide synthase inhibitor, venglustat (also known as GZ/SAR402671), in individ- uals with early PD with *GBA* mutation. This study is anticipated to enrol 243 participants and is estimated to conclude in 2022.

Despite the advances made in linking GBA to PD, not all patients with *GBA* mutations will develop parkin- sonism. Hence, improvement of our understanding of the pathological mechanisms underlying *GBA* mutation is important before patient selection for future clinical trials. In addition, the level of GBA activation needed to achieve disease modification remains unclear, and no specific biomarker is currently available to confirm target engagement with small-molecule chaperones or glucosylceramide synthase inhibitors. Furthermore, the generalizability of similar therapies to idiopathic PD remains unclear.

Neuronal rescue

Neuronal vulnerability and calcium as a therapeutic target.—The concept of differing neuronal vulnerabil- ity within different cell populations emerged from the observation of selective dopaminergic neuronal loss in the SNc relative to other areas of the parkinsonian brain[75]. Little is known about why these neurons are particularly sensitive, but they possess several properties that probably render them more susceptible to age, spe- cific

mutations and/or environmental toxins than other neuronal populations[76]. For example, the long and highly branched axons of dopaminergic neurons, which contain numerous transmitter release sites, increase mitochon- drial oxidative stress[77]. In vivo, these neurons have slow tonic activity[78]. Slow Ca^{2+} oscillations help to maintain slow tonic spiking by generating a membrane potential oscillation that facilitates Ca^{2+} entry into mitochondria, which stimulates oxidative phosphorylation and ATP production[79,80]. This process results in high levels of cyto- solic and mitochondrial Ca^{2+} (fig. 1). Dihydropyridine, an agent that inhibits voltage-dependent Ca^{2+} channels and reduces cytosolic Ca^{2+} levels[79–81], was shown to reduce the risk of PD in some epidemiological studies[82]. Data from preclinical and clinical studies support a role for calcium channels in PD and have resulted in a 5-year, phase III, disease-modification clinical trial in patients with early- stage PD — STEADY-PD III. This trial uses isradipine, a calcium channel blocker approved by the FDA for the treatment of hypertension. An estimated 336 participants will be enrolled, and the trial completion is anticipated in 2019. The primary outcome measures will include Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total scores at baseline and 36 months, and secondary measures will include MDS- UPDRS motor scores in the 'off ' state, cognitive functions and quality of life. The inclusion criteria for this trial focus on early PD (Hoehn and Yahr ≤ 2 and participants off dopaminergic therapy at enrolment).

Iron-targeting agents.—Iron deposition in the neurons of the substantia nigra (SN) of patients with PD has been demonstrated via electron probe X-ray micro- analysis and is thought to be a disease-causing process[83]. Iron can elicit oxidative damage, which results in the generation of reactive oxygen species[84]. Removal of iron from the SN might, therefore, slow disease pro- gression. Promising results from preclinical studies suggest that iron chelators can cross the blood–brain barrier and remove excess iron[85] (fig. 1). These results have prompted the initiation of a double-blinded, ran- domized, placebo-controlled, pilot clinical trial of the iron chelator deferiprone in PD[86]. This study evaluated drug safety, brain iron content changes (by MRI) and PD clinical status (by UPDRS scores) and demonstrated that short-term deferiprone therapy for participants with PD was safe and could decrease iron in specific brain regions.

FAIRPARKII, a randomized phase II study for conserva- tive iron chelation therapy in PD, is currently recruiting. Many unresolved issues remain with the iron chelation approach, including drug dose, lack of target engage- ment biomarkers and the stage of disease chosen for patient enrolment. Whether clearing iron will result in any clinical or disease-modifying benefit also remains to be determined.

Neuroinflammation-targeting agents.—Many observa- tions from epidemiological[87,88], post-mortem[89,90], ani- mal[91], serum and CSF studies[92,93] support a therapeutic strategy of immune system alteration in PD[94]. Substantial data also suggest that neuroinflammation plays a part in cell death in PD[91]. A growing body of evidence points to the neuroprotective effect of NSAIDs in PD. A study of 293 participants with PD and 286 matched controls found that NSAID users who took more than two pills per week for at least 1 month had a reduced risk of PD compared with controls[95]. These results strengthened the

idea of a beneficial role of NSAIDs for PD. To date, however, meta-analyses have failed to confirm the link between NSAIDs and reduced risk of PD[88,96], but multi- ple studies have shown an association between ibuprofen and a decreased risk of PD[97].

Lewy bodies that are released into the extraneuronal environment have been shown to activate macrophages and microglia, which subsequently alters effector T cell populations[94,98]. Data from animal models of PD demon- strate that regulatory T (Treg) cells can help with immune tolerance and can have disease-modifying effects. Sargramostim, an FDA-approved human recombinant granulocyte–macrophage colony-stimulating factor (GM-CSF) for use in patients with cancer[99], is being tested as an anti-neuroinflammatory therapy in PD. A clinical trial using sargramostim demonstrated that it was well tolerated and that the adverse events asso- ciated with this therapy were not different in patients with PD than in those observed in other patients[100]. Sargramostim improved Treg cell function and UPDRS motor scores did not worsen over time. Results from this study came from a small population and will need to be confirmed in future larger clinical trials (fig. 1).

Several groups have demonstrated the expression of the enzyme myeloperoxidase (MPO; a known player in inflammation and degeneration) by microglial cells in brains of individuals with PD[101–103]. AZD3241 is a selective and irreversible MPO inhibitor that was able to suppress microglia and protect dopaminergic neu- rons in preclinical studies and was shown to be safe and well tolerated in phase I/II trials[104,105] Administration of AZD3241 for 8 weeks resulted in a statistically signifi- cant reduction in binding of a radioligand to the trans- locator protein (TSPO; a marker of activated microglia), which indicates that the drug was able to modulate the oxidative cellular environment in brains of individu- als with PD[105]. This therapy warrants further trials to validate clinical efficacy.

Data from preclinical studies have shown that exenatide, an approved glucagon- like peptide 1 (GLP1) agonist, can normalize dopaminergic func- tion. The agent is thought to be capable of crossing the blood–brain barrier and might provide neuroprotective effects via the GLP1 receptor[106]. Exenatide might exert its positive effects by decreasing neuroinflammation through the mitogen-associated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) pathways[107] and might have beneficial effects on mitochondrial function (fig. 1). In an RCT[108] in which patients with PD were administered exenatide for 48 weeks, participants showed significant improvement in UPDRS III scores (off medication), compared with the placebo group, but no significant differences in the UPDRS IV fluctuation scores (on medication) or other metrics such as cognition, mood, dyskinesia and quality of life. The difference in motor UPDRS score at 60 weeks between the treatment and placebo arms did not change from the difference observed at 12 weeks, which suggests a symptomatic effect rather than disease modification. Two other GLP1 agonists, liraglutide and lixisenatide, are currently being assessed for disease-modifying potential in the LixiPark RCT.

Mitochondria-targeting agents.—Mitochondria are dynamic organelles that have an important role in energy metabolism and redox homeostasis[109] and undergo fis- sion and fusion in response to changes in metabolism and environmental stress[110]. Excessive

mitochondrial fragmentation has been implicated in the pathology of sporadic and familial PD, and many genes associated with familial PD have been shown to affect key components of the mitochondrial respiratory chain and to contribute to neuronal death[111] (Table 1).

Therapies that target mitochondria can be specific to their fission and/or fusion or target oxidative stress pathways (Table 3). Peroxisome proliferator-activated receptor-γ (PPARγ) is a ligand-activated transcription factor that is expressed on neurons, astrocytes and microglia. This protein belongs to the nuclear hormone receptor superfamily and has a role in redox balance, mitochondrial function and immune regulation. PPARγ agonists such as pioglitazone inhibit neuroinflammation and decrease the levels of COX2 (also known as PTGS2), suppress inducible nitric oxide synthase and cytokines such as tumour necrosis factor, reduce apoptosis and inhibit proteasomal dysfunction[112] (fig. 1). In animal models, pioglitazone has been shown to increase mito- chondrial biogenesis, leading to a reduction in neuro- degeneration[113]. US National Institute of Neurological Disorders and Stroke (NINDS) Exploratory Trials in Parkinson's Disease (NET-PD) FS-ZONE investiga- tors performed a phase II, multicentre, double-blinded RCT using pioglitazone in early PD[114]. The results revealed that pioglitazone was not effective in slowing progression of PD.

In large prospective epidemiological studies, high plasma levels of urate were associated with a low risk of PD[115,116]. Additionally, in a rat model of PD, urate pre- vented dopaminergic neuronal loss in the SN[117]. These findings facilitated the initiation of a safety and tolera- bility study for inosine, a urate precursor and potential antioxidant, in patients with PD. Inosine was shown to be effective in raising serum and CSF levels of urate[118]. SURE-PD3, an ongoing phase III RCT, was designed to investigate the role of inosine in early PD. The pri- mary outcome is change in total UPDRS scores over 24 months. Oxidative stress pathways remain an appeal- ing target despite the failure of multiple previous clin- ical trials. Table 3 summarizes major trials targeting oxidative stress and mitochondrial pathways, treatment challenges and future directions.

Symptomatic non-dopaminergic agents

Neurotransmitters such as acetylcholine, serotonin (5-hydroxytryptamine (5-HT)), noradrenaline, GABA, adenosine and glutamate play an essential part in PD symptomatology and might be involved in dopamine- resistant motor symptoms. Table 4 summarizes the dif- ferent neurotransmitter systems and their involvement in tremors, disorders of gait (particularly freezing of gait and falls), motor fluctuations and dyskinesias. figure 2 illustrates the different networks and neurotransmitters involved in motor symptoms of PD and the therapies targeted to these systems.

Tremors.—The classic tremor in PD occurs at rest and can re-emerge at posture. Tremor is considered a clin- ically unique feature of PD as it seems to correlate less with dopamine deficit than do bradykinesia and rigidity. The origin and the circuitry of tremor in the brain represent an area of active research. Basal ganglia dys- function is thought to trigger the tremor, whereas the cerebellothalamocortical circuit might act to control the tremor amplitude[119]. Tremor in patients with PD may or may not respond to dopamine treatment,

and in some patients tremor can worsen after treatment with levodopa. These findings suggest that other neuro- transmitters might be involved, including acetylcholine or 5-HT[120]. Anticholinergics such as trihexyphenidyl are useful in a subset of patients, but neuropsychiatric and cognitive adverse effects have been common reasons for withdrawal[121]. Clozapine, a potent antipsychotic used to treat PD hallucinations, can also be effective in con- trolling PD tremors[122,123]. Clozapine is a 5-HT1A receptor agonist and a 5-$HT_{2A/2C}$ receptor antagonist in addition to having antidopaminergic, anticholinergic and anti- histaminergic effects[124]. The small but serious risk of agranulocytosis remains the major drawback of using clozapine for treatment of dopamine-resistant tremors. β-Blockers have also been used with variable success in controlling parkinsonian tremor[125,126].

Gait.—Freezing of gait can be either levodopa sensitive or levodopa resistant, which suggests the involvement of non-dopaminergic networks and neurotransmitters in PD-related gait disorders. Physiology of freezing of gait involves a dorsal (cognitive) and a ventral (emo- tional) locomotor network in addition to multiple non-dopaminergic neurotransmitter systems. These sys- tems include the cholinergic, glutamatergic, noradrener- gic and GABAergic systems, among others[127]. To explore the involvement of the cholinergic system in gait dys- function in PD, investigators from the UK initiated the ReSPonD trial, a phase II RCT that tested the efficacy of the cholinesterase inhibitor rivastigmine in patients with PD who had fallen. The study revealed that rivastigmine improved gait stability and decreased chances of falls in patients with PD[128]. Another study has confirmed the role of the central cholinesterase inhibitor, donepezil, in reducing the frequency of falls in patients with PD[129]. Larger controlled trials will be needed to confirm the efficacy of cholinesterase inhibitors. Serotonergic and noradrenergic networks are affected in PD owing to degeneration of the raphe nucleus and locus coeruleus, respectively, and are implicated in gait disorders. In a double-blind, multicentre, placebo-controlled trial, methylphenidate improved hypokinesia and freezing of gait in patients with advanced PD who received sub- thalamic nucleus (STN) stimulation[130]. Methylphenidate and atomoxetine are currently being tested for effects on gait in the TAME-PD trial (fig. 2).

Motor fluctuations and dyskinesia.—Motor fluctua- tions and dyskinesia are troublesome adverse effects that result from a combination of PD progression and dopaminergic treatment. An estimated 40% of patients with PD who receive levodopa treatment develop motor fluctuations after 4–6 years of treatment[131]. Several options exist to treat these complications. The most common include adjustment of the dose, frequency of administration or type of the dopaminergic medica- tion administered. Progression of these symptoms and fluctuations can trigger consideration of other surgical options (including DBS or levodopa–carbidopa intesti- nal gel). Multiple non-dopaminergic compounds sum- marized in Table 4 have been, or are currently being, investigated for an effect on motor fluctuations.

Adenosine (A2A) receptor antagonists can improve motor functions in animal models of PD[132]. However, in two phase III RCTs, the A2A receptor antagonist prelade- nant, used as an adjunctive therapy, did not improve the motor function or reduce ‘off ‘ time in patients with PD compared with placebo or rasagiline[133,134]. Preladenant has also failed as a

monotherapy in patients with early PD in another phase III trial[135]. Given the results of these phase III studies, Merck discontinued preladenant in 2013. In contrast to preladenant, the A2A receptor antag- onist istradefylline was tested in several RCTs[136–138], and a meta-analysis suggested that it can be useful to alleviate ‘off ‘ time and motor fluctuations, although the effect on dyskinesia was not clear[139]. Development of tozadenant (another A_{2A} receptor antagonist) was halted in 2017 after reports of agranulocytosis.

Evidence suggests that 5-HT has a role in levodopa- induced dyskinesia (LID)[140]. Findings from animal models indicate that serotonergic receptor agonists can reduce motor fluctuations and LID[141]. Multiple seroton- ergic receptor agonists or antagonists are being tested in clinical trials for their effects on motor fluctuations and dyskinesia (Table 4). Similarly, glutamate has been implicated in motor fluctuations in patients with PD, and *N*-methyl-d-aspartate (NMDA) receptor antagonists such as amantadine have been used with variable suc- cess for the treatment of dyskinesia[142]. However, systemic and nonmotor adverse effects (cognitive and psychiat- ric) limit their use. Therapies with increased selectivity against metabotropic glutamate receptors are being tested for their effects on motor complications[143] (Table 4).

Non-pharmacotherapeutic interventions

Gene therapy

The aim of gene therapy is to replace, silence or mod- ify mutated genes with the use of non-replicating viral vectors such as adeno-associated virus (AAV) or lenti- virus. Several studies in humans have shown that these viruses are safe and efficient for gene delivery[144–147]. One of the advantages of this approach is the ability to deliver therapies to specific brain regions, thereby reducing off- target effects. Disadvantages include the difficulty in regulating the amount of therapy delivered and the fact that the therapy might be irreversible. Here, we discuss viral vector-mediated targeted delivery of genes encod- ing proteins involved in dopamine production (such as aromatic-l-amino acid decarboxylase (AADC)) or basal ganglia network modulation (such as glutamate decarboxylase (GAD)) for symptomatic motor therapy. We also discuss neurotrophic factors and gene therapy for potential disease modification. Table 5 summarizes clinical trials, major advances in the field, outcomes and challenges of these treatment strategies.

Dopamine restoration.—AADC is an enzyme that con- verts 3,4-dihydroxyphenylalanine (l-DOPA) to dopa- mine and thereby enables endogenous stimulation of dopamine production in surviving neurons in PD. AADC has been shown to enable decarboxylation of l-DOPA by an AAV delivery approach[148] and has resulted in behavioural recovery[149] in preclinical models. Studies that use vectors for single-enzyme AADC are summarized in Table 5. A safety study of VY-AADC01, an investigational agent administered via injection into the putamen of patients with PD, is anticipated to con- clude by the end of 2019. Initial reports have shown that VY-AADC01 is well tolerated and has no serious adverse events[150]. The study is using a higher vector genome concentration than was used in previous AADC gene therapy trials and is employing real-time MRI to mon- itor vector delivery. Potential clinical and radiological responses will also be assessed.

ProSavin is a viral vector containing three genes encoding enzymes required for making dopamine: tyrosine 3-monooxygenase, AADC and GTP cyclohy- drolase 1. Results from the study showed an improve- ment in motor symptoms in patients with PD 12 months after treatment and prompted the launch of OXB-102, a second-generation gene therapy (an approach that uses a vector encoding the same enzymes but that enables greater dopamine production). Preliminary results from animal studies showed superior efficacy of OXB-102 compared with ProSavin and supported further clinical development. Success in the phase I study has led to the launch of the phase II Axo-Lenti-PD trial (also known as SUNRISE-PD trial). The trial has an open-label dose escalation phase of OXB-102 and a randomized double- blinded phase. The primary outcome remains the safety of the compound, but secondary outcome measures will focus on UPDRS scores 'on' and 'off' medica- tions and motor fluctuations at 6 months. Preliminary results from the first two enrolled patients are expected in March 2019.

Basal ganglia network modulation.—In patients with PD, nigrostriatal degeneration leads to an excessive inhibi- tory output from the globus pallidus internus (GPi) and substantia nigra reticulata (SNr) as a result of disinhibi- tion of the STN, which is thought to drive the GPi and SNr via release of glutamate. This pathway suggests that enhancement of GABA transmission from the STN and its terminal regions via GAD could be of therapeutic benefit. AAV-GAD administration to the STN resulted in improvements in bradykinesia, gross motor skills and tremor in non-human primate models of PD[151]. Following these promising animal studies, Neurologix announced a gene therapy trial, NLX-P101, that is based on the introduction of a gene encoding GAD into brain cells via AAV. Symptom improvement was reported in patients with PD on the basis of UPDRS scores 6 months after the administration of AAV-GAD (Table 5). The 12-month clinical effects of bilateral STN delivery of GAD revealed persistent improvement of the UPDRS motor scores in the treatment group compared with the sham group[152]. A significant reduction in the daily duration of LID was also observed in the treatment group.

Neurotrophic factors.—The mechanism by which neu- rotrophic factors elicit their neuroprotective effect is poorly understood. However, several studies have shown that neurotrophic factors can induce beneficial effects on dopaminergic neurons[153,154].

As a survival factor for dopaminergic neurons of the midbrain region[155], glial-derived neurotrophic factor (GDNF) is an attractive target for slowing the course of degeneration. The beneficial effects of GDNF have been demonstrated in animal models[156,157]. A phase II double- blinded, placebo-controlled study of a continuous infu- sion of GDNF into the putamen of patients with PD was conducted by Amgen. Study results showed that the therapy was well tolerated. However, it did not meet the primary end point as no significant improvements in UPDRS scores were observed and the study was halted for long-term safety reasons. In 2013, a 5-year phase I trial of AAV2-GDNF was launched. The trial is currently active, but no results are available.

A close homologue of GDNF, neurturin (NRTN), is another potential therapy[158]. Injections of recombinant NRTN have demonstrated variable results in animal models of PD[159–161]. CERE-120 (also known as AAV2- neurturin; developed by Ceregene) was tested in patients

with PD in the first trial of a gene therapy using a neuro- trophic factor. Phase I study results showed improve- ment in UPDRS scores in patients with PD[162]. A phase II study was subsequently launched, but no significant differences were found between treatment groups in the primary end point measured by the UPDRS scores[163] (fig. 1; Table 5).

Failure of GDNF and NRTN to show clinical benefits precipitated a search for alternative neurotrophic factors for PD. Cerebral dopamine neurotrophic factor (CDNF) was neuroprotective for midbrain dopaminergic neurons in a rat model of PD[164], and a phase I/II trial is currently evaluating the safety and efficacy of direct putamen infu- sion in patients with PD (Table 5). Other neurotrophic factors, such as brain-derived neurotrophic factor and vascular endothelial growth factor, are currently in the preclinical pipeline[165,166].

In summary, gene therapy is a promising avenue for treatment of PD, and successful advances have been made in dopamine restoration and sympto- matic therapies, although disease modification with trophic factors has not yet been shown to be feasible in humans. Challenges that limit these therapies include the potential need to deliver a combination of neuro- trophic factors, the determination of best targets and the improvement in delivery methods.

Cellular therapies

The field of cell transplantation did not start to gain momentum as a potential therapy for PD until after the development of the 6-hydroxydopamine-lesioned rat model of PD in the late 1970s[167]. Assessment of the thera- peutic potential of cell transplantation in the lesioned rodent brain was made possible by the development of this model. Early experiments in the 1980s transplanted adrenal medullary cells (which can produce catechola- mines such as dopamine) into the striatum of patients with PD. However, these transplants were deemed futile and unsafe[167]. Transplantation trials of mesencephalic dopaminergic neurons obtained from fetuses showed positive effects but had ethical and safety challenges. Alternative and potentially promising cell therapies have included dopaminergic cells derived from human pluripotent stem cells (hPSCs), which could be either human embryonic stem cells (hESCs) or induced pluri- potent stem cells (iPSCs). Despite all of the advances made in the field of cellular transplant in the past few decades, dopaminergic cell replacement therapy for PD is still considered a symptomatic therapy rather than a disease-modifying intervention[168].

Mesencephalic fetal cell transplantation.—Open-label studies showed that transplantation of mesencephalic fetal dopaminergic neurons into the striatum of patients with PD improved motor symptoms and reduced motor fluctuations, presumably by restoring striatal dopa- minergic transmission[169]. Subsequent RCTs failed to demonstrate meaningful clinical improvement, and graft-induced ‘runaway’ dyskinesias (that is, post-transplantation dyskinesias that occur even after a prolonged absence of antiparkinsonian medication[170]) were reported[171,172], thereby halting further trials. The mechanism of the runaway dyskinesias remains uncer- tain and is yet to be fully elucidated. Despite adverse effects, young patients[171] with low disease burden[172] and individuals free from pre-intervention dyskinesias had improved outcomes. This observation contributed to the launch the European consortium TRANSEURO to globally evaluate fetal mesencephalic cell

transplant in PD. However, tissue availability and the ethical dilemma of using fetal tissue in research[167] are challenges that still need to be addressed (fig. 3).

Stem cell therapy.—In 2006, dopaminergic neurons derived from hESCs were implanted intrastriatally in an animal model of PD and resulted in behavioural improvements[173]. Subsequently, several researchers have worked to refine the conversion process of hESCs to dopaminergic cells by improving specification[174]. When grafted, these cells modulated neurotransmis- sion in a rodent model of PD, retained the ability to sur- vive long term and grew and functioned efficiently[175]. Notwithstanding, the therapy has safety limitations that need to be addressed before human application (fig. 3).

Another approach to neuronal restoration is to use a cocktail of transcription factors to reprogramme skin or blood cells to become iPSCs or induced neurons[176]. This technique would facilitate the generation of patient- specific transplantable cells, which could circumvent immune rejection as well as other ethical issues that surround hESCs. Successful iPSC transplantation in monkeys has led to plans for a clinical trial employing iPSCs in patients with PD that has already commenced in Kyoto, Japan[177].

Results from clinical trials have shown that grafted cells are capable of long-term survival and are able to integrate into appropriate functional brain networks. Advances in iPSC research have now made it feasible to move these applications towards the clinical environment. The international GForce-PD initiative connected centres from the USA, Europe and Japan for the clinical application of hPSCs in PD. Many collaborative efforts are being planned for the next 2 years: the EUROPEAN STEM-PD, which comprises two European consortia (TRANSEURO, which will use fetal mesencephalic cells, and NeuroStemCellRepair, which will use hESCs); NYSTEM-PD (New York State Stem Cell Science), which will use hESCs; CiRA (Center for iPS Cell Research and Application, Kyoto University, Japan), which will use allogeneic iPSCs; and a Summit for Stem Cell trial, which will use autologous iPSCs[178]. Outside of this initia- tive, a few open-label clinical trials are already recruiting, including a phase I/II trial to assess safety and efficacy of striatum transplantation of hESC-derived neural pre- cursor cells in patients with PD[179]. An important consid- eration is that stem cell therapies remain experimental, and commercial stem cell tourism is a major challenge for the field as unapproved cell-based therapies are being administered peripherally or directly into the CNS and can lead to serious complications[168]. Additionally, the stem cell transplantation field will probably be limited by many of the same challenges that previous transplan- tation studies have encountered. Perhaps the biggest challenge remains the failure to address degeneration in multiple motor and nonmotor pathways.

Deep brain stimulation

A new era for neural network modulation began in 1987, when Alim Benabid implanted the first DBS electrode for the treatment of a patient with tremor[180]. Wide appli- cation of DBS to PD first began in the early 1990s, and since then the procedure has improved the treatment of PD. Multiple RCTs have demonstrated the benefits of DBS for improving motor symptoms, fluctuations (that is, ‘off ‘ time) and quality of life compared with medical

therapy alone[181–184]. The two main targets in PD, the GPi and STN, have provided similar motor benefits[185], with the choice of target often dictated by patient profile and goals of treatment. Despite the substantial advances in the field of neuromodulation, dopaminergic-resistant symptoms such as axial symp- toms (affecting gait, balance, posture and speech) poorly respond to current DBS technologies[186]. Novel approaches include stimulation of different networks, use of alternative hardware (directional DBS leads), adaptive DBS and use of advanced imaging for more individualized targeting[187]. Non-invasive DBS and opto-genetically inspired DBS are promising therapies on the horizon.

New targets.—The pedunculopontine nucleus (PPN) has emerged as a target for DBS after animal studies showed that stimulation yielded improvements in akinesia and gait[188]. Initial positive reports on gait dysfunction and postural instability in patients with PD[189,190] drove clini- cal trials for further evaluation of the effects of PPN-DBS on gait and freezing. Results have been suboptimal owing to several factors, including a limited number of patients, variation in methodology, inconsistent definition of freezing in patients with PD, imprecise definition of the location of stimulation and poor choice of stimulation programming parameters. The SNr has also been eva- luated as a target to improve refractory axial symptoms and has shown promising results[191,192]. Several other DBS targets have been emerging for treatment of motor symptoms (including the zona incerta, posterior subtha-lamic area and centromedian thalamus). Further analy- sis of results that establish common standard protocols for targeting and programming will be needed.

Adaptive DBS and individualized targeting.—Adaptive DBS is a responsive DBS system that is capable of sens- ing physiological signals and auto-adjusting stimula- tion, which could improve clinical benefit, limit adverse effects and reduce neurostimulation battery costs. The most challenging aspect of this therapy has been detec- tion of a reliable physiological signal to target. Beta band activity has been the most studied physiological signal, but more work will be needed to assess its reliability[193]. Individualization of DBS therapy utilizing diffusion tensor imaging and functional MRI to identify appro- priate networks for planning targets has the potential to improve clinical DBS outcomes.

Non-invasive and optogenetically inspired DBS.—A method for non-invasive DBS has emerged through the application of temporal interference. Temporal interfer- ence consists of the application of two overlapping electric fields of different frequencies via an external device. The difference in frequencies in the overlap region of the two fields delivers stimulation deep in the brain, without inter- rupting the function of superficial structures[194]. This tech- nique remains at a preclinical level but has the potential to reduce the risks associated with invasive DBS (fig. 4).

Optogenetics, a technique that uses light to control genetically modified neurons expressing light-sensitive ion channels and pumps, has gained interest in the past few years (fig. 4). Optogenetically defined DBS for the GPe has demonstrated the feasibility of exciting or inhibiting different cells types to enhance the treatment response in animals[195]. Identification of suitable targets and precise light delivery with penetration to deep brain structures remain challenges for this therapy. One study successfully demonstrated that upconversion nanopar- ticles can absorb near-infrared light emitted outside the brain to

convert it into local emission of visible light and stimulate deep brain structures (fig. 4). This approach could facilitate the process of less invasive optogenetic manipulation of neuronal activity[196]. The safety of these nanoparticles in humans remains to be established.

Potential for disease modification.—Evidence from animal models has suggested the possibility of the neuroprotec- tive effects of STN-DBS. However, results from clinical trials have yet to support this notion. STN-DBS did not protect the nigrostriatal system against α-synuclein- mediated toxicity, according to one study[197]. Delivery of autologous nerve grafts (as a source of neurotrophic factors) to the SNr during STN-DBS surgery has been another approach used in an open-label trial[198], but larger trials are needed to evaluate the efficacy and disease-modifying potential of this strategy. This new approach has been termed DBS-plus.

Conclusions

PD is associated with a range of pathophysiological processes, including α-synuclein aggregation, neu- roinflammation, mitochondrial dysfunction, neuronal vulnerability, iron deposition and neural network alter- ations. The complexity of these intertwined pathways and the heterogeneity in clinical phenotypes will require a targeted approach for therapy. Although current treat- ment options provide symptomatic relief, advances in high-throughput screening methods for small mol- ecules, improved disease modelling and progress in analytical technologies are likely to facilitate novel compounds and repurposed drugs. Immunotherapies could provide a novel mechanism for the body to boost its response to α-synuclein. Research in the field of cell-based therapies has provided an improved com-prehension of the disease, and some iPSC therapies could be used in personalized therapy. Adaptive DBS and optogenetically inspired DBS might aid the defi- nition of more specific targets. Taken together, these advancements suggest that the future of PD therapies is promising.

Acknowledgements

The authors are supported by NIH grants R01 NR014852 and R01NS096008; NIH/National Center for Advancing Translational Sciences Clinical and Translational Science Awards to the University of Florida (UL1TR001427, KL2TR001429 and TL1TR001428); and the Parkinson’s Foundation.

References

1. Kalia LV & Lang AE Parkinson’s disease. Lancet 386, 896–912 (2015). [PubMed: 25904081]
2. Lang AE & Espay AJ Disease modification in Parkinson’s disease: current approaches, challenges, and future considerations. Mov. Disord 33, 660–677 (2018). [PubMed: 29644751]
3. Van Rooden SM et al. The identification of Parkinson’s disease subtypes using cluster analysis: a systematic review. Mov. Disord 25, 969–978 (2010). [PubMed: 20535823]
4. Marras C & Lang A Parkinson’s disease subtypes: lost in translation? J. Neurol. Neurosurg. Psychiatry 84, 409–415 (2013). [PubMed: 22952329]
5. Schapira AHV, Chaudhuri KR & Jenner P Non-motor features of Parkinson disease. Nat. Rev. Neurosci 18, 435–450 (2017). [PubMed: 28592904]
6. Chaudhuri KR, Healy DG & Schapira AHV Non-motor symptoms of Parkinson’s disease: diagnosis and management. Lancet Neurol. 5, 235–245 (2006). [PubMed: 16488379]

7. Pfeiffer RF Non-motor symptoms in Parkinson's disease. Parkinsonism Relat. Disord 22, S119–S122 (2016). [PubMed: 26372623]
8. Polymeropoulos MH et al. Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047 (1997). [PubMed: 9197268]
9. Spillantini MG et al. α-Synuclein in Lewy bodies. Nature 388, 839–840 (1997). [PubMed: 9278044]
10. Bendor JT, Logan TP & Edwards RH The function of α-synuclein. Neuron 79, 1044–1066 (2013). [PubMed: 24050397]
11. Wong YC & Krainc D α-Synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies. Nat. Med 23, 1–13 (2017).
12. Dehay B et al. Targeting α-synuclein for treatment of Parkinson's disease: mechanistic and therapeutic considerations. Lancet Neurol. 14, 855–866 (2015). [PubMed: 26050140]
13. Conway KA, Harper JD & Lansbury PT Accelerated in vitro fibril formation by a mutant α-synuclein linked to early-onset Parkinson disease. Nat. Med 4, 1318–1320 (1998). [PubMed: 9809558]
14. Cuervo AM, Stefanis L, Fredenburg R, Lansbury PT & Sulzer D Impaired degradation of mutant α-synuclein by chaperone-mediated autophagy. Science 305, 1292–1295 (2004). [PubMed: 15333840]
15. Martinez-Vicente M et al. Dopamine-modified α-synuclein blocks chaperone-mediated autophagy. J. Clin. Invest 118, 777–788 (2008). [PubMed: 18172548]
16. Chinta SJ, Mallajosyula JK, Rane A & Andersen JK Mitochondrial alpha-synuclein accumulation impairs complex I function in dopaminergic neurons and results in increased mitophagy in vivo. Neurosci. Lett 486, 235–239 (2010). [PubMed: 20887775]
17. Guardia-Laguarta C et al. α-Synuclein is localized to mitochondria-associated ER membranes. J. Neurosci 34, 249–259 (2014). [PubMed: 24381286]
18. Paillusson S et al. α-Synuclein binds to the ER–mitochondria tethering protein VAPB to disrupt Ca^{2+} homeostasis and mitochondrial ATP production. Acta Neuropathol. 134, 129–149 (2017). [PubMed: 28337542]
19. Olanow CW & Kordower JH Targeting α-synuclein as a therapy for Parkinson's disease: the battle begins. Mov. Disord 32, 203–207 (2017). [PubMed: 28218461]
20. Mittal S et al. β2-Adrenoreceptor is a regulator of the alpha-synuclein gene driving risk of Parkinson's disease. Science 357, 891–898 (2017). [PubMed: 28860381]
21. Searles Nielsen S, Gross A, Camacho-Soto A, Willis AW & Racette BA β2-adrenoreceptor medications and risk of Parkinson disease. Ann. Neurol 84, 683–693 (2018). [PubMed: 30225948]
22. Webb JL, Ravikumar B, Atkins J, Skepper JN & Rubinsztein DC α-Synuclein is degraded by both autophagy and the proteasome. J. Biol. Chem 278, 25009–25013 (2003). [PubMed: 12719433]
23. Lee BH et al. Enhancement of proteasome activity by a small-molecule inhibitor of USP14. Nature 467, 179–184 (2010). [PubMed: 20829789]
24. Dehay B et al. Pathogenic lysosomal depletion in Parkinson's disease. J. Neurosci 30, 12535–12544 (2010). [PubMed: 20844148]
25. Torra A et al. Overexpression of TFEB drives a pleiotropic neurotrophic effect and prevents Parkinson's disease-related neurodegeneration. Mol. Ther 26, 1552–1567 (2018). [PubMed: 29628303]
26. Xilouri M, Brekk OR, Kirik D & Stefanis L LAMP2A as a therapeutic target in Parkinson disease. Autophagy 9, 2166–2168 (2013). [PubMed: 24145820]
27. Spencer B et al. Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in -synuclein models of Parkinson's and Lewy body diseases. J. Neurosci 29, 13578–13588 (2009). [PubMed: 19864570]
28. Malagelada C, Jin ZH, Jackson-Lewis V, Przedborski S & Greene LA Rapamycin protects against neuron death in in vitro and in vivo models of Parkinson's disease. J. Neurosci 30, 1166–1175 (2010). [PubMed: 20089925]
29. Karuppagounder SS et al. The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci. Rep 4, 4874 (2014). [PubMed: 24786396]

30. Pagan F et al. Nilotinib effects in Parkinson's disease and dementia with lewy bodies. J. Parkinsons Dis 6, 503–517 (2016). [PubMed: 27434297]
31. Simuni T et al. A phase 2a study of nilotinib in patients with advanced and early Parkinson's disease. study design [abstract]. Mov. Disord 33 (Suppl. 2), 238 (2018). [PubMed: 29278288]
32. Savolainen MH et al. The beneficial effect of a prolyl oligopeptidase inhibitor, KYP-2047, on α-synuclein clearance and autophagy in A30P transgenic mouse. Neurobiol. Dis 68, 1–15 (2014). [PubMed: 24746855]
33. Myöhänen TT et al. A prolyl oligopeptidase inhibitor, KYP-2047, reduces α-synuclein protein levels and aggregates in cellular and animal models of Parkinson's disease. Br. J. Pharmacol 166, 1097–1113 (2012). [PubMed: 22233220]
34. Perni M et al. A natural product inhibits the initiation of α-synuclein aggregation and suppresses its toxicity. Proc. Natl Acad. Sci. USA 114, E1009–E1017 (2017). [PubMed: 28096355]
35. Richter F et al. A molecular tweezer ameliorates motor deficits in mice overexpressing α-synuclein. Neurotherapeutics 14, 1107–1119 (2017). [PubMed: 28585223]
36. Recasens A et al. Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. Ann. Neurol 75, 351–362 (2014). [PubMed: 24243558]
37. Kordower JH, Chu Y, Hauser RA, Freeman TB & Olanow CW Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat. Med 14, 504–506 (2008). [PubMed: 18391962]
38. Volpicelli-Daley LA et al. Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. Neuron 72, 57–71 (2011). [PubMed: 21982369]
39. Paumier KL et al. Intrastriatal injection of pre- formed mouse α-synuclein fibrils into rats triggers α-synuclein pathology and bilateral nigrostriatal degeneration. Neurobiol. Dis 82, 185–199 (2015). [PubMed: 26093169]
40. Mao X et al. Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science 353, aah3374 (2016). [PubMed: 27708076]
41. Masliah E et al. Effects of α-synuclein immunization in a mouse model of Parkinson's disease. Neuron 46, 857–868 (2005). [PubMed: 15953415]
42. Masliah E et al. Passive immunization reduces behavioral and neuropathological deficits in an alpha-synuclein transgenic model of lewy body disease. PLOS ONE 6, e19338 (2011). [PubMed: 21559417]
43. Bae E-J et al. Antibody-aided clearance of extracellular -synuclein prevents cell-to-cell aggregate transmission. J. Neurosci 32, 13454–13469 (2012). [PubMed: 23015436]
44. Mandler M et al. Next-generation active immunization approach for synucleinopathies: Implications for Parkinson's disease clinical trials. Acta Neuropathol 127, 861–879 (2014). [PubMed: 24525765]
45. Jankovic J et al. Safety and tolerability of multiple ascending doses of PRX002/RG7935, an anti—synuclein monoclonal antibody, in patients with Parkinson disease: a randomized clinical trial. JAMA Neurol. 75, 1206–1214 (2018). [PubMed: 29913017]
46. Schneeberger A, Tierney L & Mandler M Active immunization therapies for Parkinson's disease and multiple system atrophy. Mov. Disord 31, 214–224 (2016). [PubMed: 26260853]
47. Poulopoulos M, Levy OA & Alcalay RN The neuropathology of genetic Parkinson's disease. Mov. Disord 27, 831–842 (2012). [PubMed: 22451330]
48. Doherty KM et al. Parkin disease: a clinicopathologic entity? JAMA Neurol. 70, 571–579 (2013). [PubMed: 23459986]
49. Blanz J & Saftig P Parkinson's disease: acid- glucocerebrosidase activity and alpha-synuclein clearance. J. Neurochem 139 (Suppl. 1), 198–215 (2016). [PubMed: 26860955]
50. Frigerio R et al. Incidental Lewy body disease: do some cases represent a preclinical stage of dementia with Lewy bodies? Neurobiol. Aging 32, 857–863 (2011). [PubMed: 19560232]
51. West AB Achieving neuroprotection with LRRK2 kinase inhibitors in Parkinson disease. Exp. Neurol 298, 236–245 (2017). [PubMed: 28764903]

52. Satake W et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nat. Genet 41, 1303–1307 (2009). [PubMed: 19915576]
53. Simón-Sánchez J et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat. Genet 41, 1308–1312 (2009). [PubMed: 19915575]
54. Nalls MA et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat. Genet 46, 989–993 (2014). [PubMed: 25064009]
55. Martin I, Kim JW, Dawson VL & Dawson TM LRRK2 pathobiology in Parkinson's disease. J. Neurochem 131, 554–565 (2014). [PubMed: 25251388]
56. Esteves AR, Swerdlow RH & Cardoso SM LRRK2, a puzzling protein: insights into Parkinson's disease pathogenesis. Exp. Neurol 261, 206–216 (2014). [PubMed: 24907399]
57. Cresto N et al. The unlikely partnership between LRRK2 and α-synuclein in Parkinson's disease. Eur. J. Neurosci 10.1111/ejn.14182 (2018).
58. Henderson MX, Peng C, Trojanowski JQ & Lee VMY LRRK2 activity does not dramatically alter α-synuclein pathology in primary neurons. Acta Neuropathol. Commun 6, 45 (2018). [PubMed: 29855356]
59. Healy DG et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 7, 583–590 (2008). [PubMed: 18539534]
60. Sardi SP, Cedarbaum JM & Brundin P Targeted therapies for Parkinson's disease: from genetics to the clinic. Mov. Disord 33, 684–696 (2018). [PubMed: 29704272]
61. Ness D et al. Leucine-rich repeat kinase 2 (LRRK2)- deficient rats exhibit renal tubule injury and perturbations in metabolic and immunological homeostasis. PLOS ONE 8, e66164 (2013). [PubMed: 23799078]
62. Herzig MC et al. LRRK2 protein levels are determined by kinase function and are crucial for kidney and lung homeostasis in mice. Hum. Mol. Genet 20, 4209–4223 (2011). [PubMed: 21828077]
63. Fuji RN et al. Effect of selective LRRK2 kinase inhibition on nonhuman primate lung. Sci. Transl Med 7, 273ra15 (2015).
64. Fan Y et al. Interrogating Parkinson's disease LRRK2 kinase pathway activity by assessing Rab10 phosphorylation in human neutrophils. Biochem. J 475, 23–44 (2017).
65. Di Maio R et al. LRRK2 activation in idiopathic Parkinson's disease. Sci. Transl Med 10, eaar5429 (2018). [PubMed: 30045977]
66. Tayebi N et al. Gaucher disease with parkinsonian manifestations: Does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? Mol. Genet. Metab 79, 104–109 (2003). [PubMed: 12809640]
67. Sidransky E et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N. Engl. J. Med 361, 1651–1661 (2009). [PubMed: 19846850]
68. Brockmann K et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov. Disord 30, 407–411 (2015). [PubMed: 25448271]
69. Choi JH et al. Aggregation of α-synuclein in brain samples from subjects with glucocerebrosidase mutations. Mol. Genet. Metab 104, 185–188 (2011). [PubMed: 21742527]
70. Mazzulli JR et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 146, 37–52 (2011). [PubMed: 21700325]
71. Bendikov-Bar I, Maor G, Filocamo M & Horowitz M Ambroxol as a pharmacological chaperone for mutant glucocerebrosidase. Blood Cells Mol. Dis 50, 141–145 (2013). [PubMed: 23158495]
72. Lieberman RL, D'Aquino JA, Ringe D & Petsko GA Effects of pH and iminosugar pharmacological chaperones on lysosomal glycosidase structure and stability. Biochemistry 48, 4816–4827 (2009). [PubMed: 19374450]
73. McNeill A et al. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain 137, 1481–1495 (2014). [PubMed: 24574503]
74. Sardi SP et al. Glucosylceramide synthase inhibition alleviates aberrations in synucleinopathy models. Proc. Natl Acad. Sci. USA 114, 2699–2704 (2017). [PubMed: 28223512]

75. Double DL, Reyes R, Werry WL & Halliday HM Selective cell death in neurodegeneration: why are some neurons spared in vulnerable regions? Prog. Neurobiol 92, 316–329 (2010). [PubMed: 20541584]
76. Surmeier DJ, Obeso JA & Halliday GM Selective neuronal vulnerability in Parkinson disease. Nat. Rev. Neurosci 18, 101–113 (2017). [PubMed: 28104909]
77. Pacelli C et al. Elevated mitochondrial bioenergetics and axonal arborization size are key contributors to the vulnerability of dopamine neurons. Curr. Biol 25, 2349–2360 (2015). [PubMed: 26320949]
78. Surmeier DJ & Schumacker PT Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease. J. Biol. Chem 288, 10736–10741 (2013). [PubMed: 23086948]
79. Sanchez-Padilla J et al. Mitochondrial oxidant stress in locus coeruleus is regulated by activity and nitric oxide synthase. Nat. Neurosci 17, 832–840 (2014). [PubMed: 24816140]
80. Guzman JN et al. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature 468, 696–700 (2010). [PubMed: 21068725]
81. Goldberg JA et al. Calcium entry induces mitochondrial oxidant stress in vagal neurons at risk in Parkinson's disease. Nat. Neurosci 15, 1414–1421 (2012). [PubMed: 22941107]
82. Gudala K, Kanukula R & Bansal D Reduced risk of Parkinson's disease in users of calcium channel blockers: a meta-analysis. Int. J. Chronic Dis 2015, 697404 (2015). [PubMed: 26464872]
83. Oakley AE et al. Individual dopaminergic neurons show raised iron levels in Parkinson disease. Neurology 68, 1820–1825 (2007). [PubMed: 17515544]
84. Ward RJ, Zucca FA, Duyn JH, Crichton RR & Zecca L The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol. 13, 1045–1060 (2014). [PubMed: 25231526]
85. Dexter DT et al. Clinically available iron chelators induce neuroprotection in the 6-OHDA model of Parkinson's disease after peripheral administration. J. Neural Transm 118, 223–231 (2011). [PubMed: 21165659]
86. Martin-Bastida A et al. Brain iron chelation by deferiprone in a phase 2 randomised double-blinded placebo controlled clinical trial in Parkinson's disease. Sci. Rep 7, 1398 (2017). [PubMed: 28469157]
87. Ton TG et al. Nonsteroidal anti-inflammatory drugs and risk of Parkinson's disease. Mov. Disord 21, 964–969 (2006). [PubMed: 16550541]
88. Gagne JJ & Power MC Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis. Neurology 74, 995–1002 (2010). [PubMed: 20308684]
89. McGeer PL, Itagaki S, Boyes BE & McGeer EG Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 38, 1285–1285 (1988). [PubMed: 3399080]
90. Mogi M et al. Interleukin-1β, interleukin-6, epidermal growth factor and transforming growth factor-α are elevated in the brain from parkinsonian patients. Neurosci. Lett 180, 147–150 (1994). [PubMed: 7700568]
91. Hirsch EC & Hunot S Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 8, 382–397 (2009). [PubMed: 19296921]
92. Dobbs RJ et al. Association of circulating TNF-α and IL-6 with ageing and parkinsonism. Acta Neurol. Scand 100, 34–41 (1999). [PubMed: 10416510]
93. Blum-Degena D et al. Interleukin-1β and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. Neurosci. Lett 202, 17–20 (1995). [PubMed: 8787820]
94. Mosley RL, Hutter-Saunders JA, Stone DK & Gendelman HE Inflammation and adaptive immunity in Parkinson's disease. Cold Spring Harb. Perspect. Med 2, a009381 (2012). [PubMed: 22315722]
95. Wahner AD, Bronstein JM, Bordelon YM & Ritz B Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease. Neurology 69, 1836–1842 (2007). [PubMed: 17984451]
96. Samii A, Etminan M, Wiens MO & Jafari S NSAID use and the risk of parkinsons disease: systematic review and meta-analysis of observational studies. Drugs Aging 26, 769–779 (2009). [PubMed: 19728750]

97. Gao X, Chen H, Schwarzschild MA & Ascherio A Use of ibuprofen and risk of Parkinson disease. Neurology 76, 863–869 (2011). [PubMed: 21368281]

98. Shameli A et al. A critical role for α-synuclein in development and function of T lymphocytes. Immunobiology 221, 333–340 (2016). [PubMed: 26517968]

99. Smith TJ et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J. Clin. Oncol 24, 3187–3205 (2006). [PubMed: 16682719]

100. Gendelman HE et al. Evaluation of the safety and immunomodulatory effects of sargramostim in a randomized, double-blind phase 1 clinical Parkinson's disease trial. NPJ Parkinsons Dis 3, 10 (2017). [PubMed: 28649610]

101. Gellhaar S, Sunnemark D, Eriksson H, Olson L & Galter D Myeloperoxidase-immunoreactive cells are significantly increased in brain areas affected by neurodegeneration in Parkinson's and Alzheimer's disease. Cell Tissue Res. 369, 445–454 (2017). [PubMed: 28466093]

102. Ouchi Y et al. Microglial activation and dopamine terminal loss in early Parkinson's disease. Ann. Neurol 57, 168–175 (2005). [PubMed: 15668962]

103. Gerhard A et al. In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. Neurobiol. Dis 21, 404–412 (2006). [PubMed: 16182554]

104. Posener JA et al. Safety, tolerability, and pharmacodynamics of AZD3241, a myeloperoxidase inhibitor, in Parkinson's disease [abstract]. Mov. Disord 29 (Suppl. 1), 698 (2014).

105. Jucaite A et al. Effect of the myeloperoxidase inhibitor AZD3241 on microglia: a PET study in Parkinson's disease. Brain 138, 2687–2700 (2015). [PubMed: 26137956]

106. Harkavyi A et al. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. J. Neuroinflammation 5, 19 (2008). [PubMed: 18492290]

107. Athauda D & Foltynie T The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action. Drug Discov. Today 21, 802–818 (2016). [PubMed: 26851597]

108. Athauda D et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double- blind, placebo-controlled trial. Lancet 390, 1664–1675 (2017). [PubMed: 28781108]

109. Yin F, Boveris A & Cadenas E Mitochondrial energy metabolism and redox signaling in brain aging and neurodegeneration. Antioxid. Redox Signal 20, 353–371 (2014). [PubMed: 22793257]

110. Twig G & Shirihai OS The interplay between mitochondrial dynamics and mitophagy. Antioxid. Redox Signal 14, 1939–1951 (2011). [PubMed: 21128700]

111. Wang W et al. Parkinson's disease-associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. Nat. Med 22, 54–63 (2016). [PubMed: 26618722]

112. Corona JC & Duchen MR PPARγ and PGC-1α as therapeutic targets in Parkinson's. Neurochem. Res 40, 308–316 (2014). [PubMed: 25007880]

113. Pinto M et al. Pioglitazone ameliorates the phenotype of a novel Parkinson's disease mouse model by reducing neuroinflammation. Mol. Neurodegener 11, 25 (2016). [PubMed: 27038906]

114. Simuni T et al. Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial. Lancet Neurol. 14, 795–803 (2015). [PubMed: 26116315]

115. De Lau LML, Koudstaal PJ, Hofman A & Breteler MMB Serum uric acid levels and the risk of Parkinson disease. Ann. Neurol 58, 797–800 (2005). [PubMed: 16240356]

116. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA & Ascherio A Plasma urate and risk of Parkinson's disease. Am. J. Epidemiol 166, 561–567 (2007). [PubMed: 17584757]

117. Gong L et al. Neuroprotection by urate on 6-OHDA- lesioned rat model of Parkinson's disease: linking to Akt/GSK3β signaling pathway. J. Neurochem 123, 876–885 (2012). [PubMed: 23094836]

118. Schwarzschild MA et al. Inosine to increase serum and cerebrospinal fluid urate in parkinson disease a randomized clinical trial. JAMA Neurol. 71, 141–150 (2014). [PubMed: 24366103]

119. Helmich RC, Janssen MJR, Oyen WJG, Bloem BR & Toni I Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. Ann. Neurol 69, 269–281 (2011). [PubMed: 21387372]

120. Doder M, Rabiner EA, Turjanski N, Lees AJ & Brooks DJ Tremor in Parkinson's disease and serotonergic dysfunction: An11C-WAY 100635 PET study. Neurology 60, 601–605 (2003). [PubMed: 12601099]

121. Katzenschlager R, Sampaio C, Costa J & Lees A Anticholinergics for symptomatic management of Parkinson's disease. Cochrane Database Syst. Rev 2, CD003735 (2002).

122. Friedman JH et al. Benztropine versus clozapine for the treatment of tremor in Parkinson's disease. Neurology 48, 1077–1081 (1997). [PubMed: 9109903]

123. Thomas AA & Friedman JH Current use of clozapine in Parkinson disease and related disorders. Clin. Neuropharmacol 33, 14–16 (2010). [PubMed: 20023573]

124. Yaw TK, Fox SH & Lang AE Clozapine in Parkinsonian rest tremor: a review of outcomes, adverse reactions, and possible mechanisms of action. Mov. Disord. Clin. Pract 3, 116–124 (2016). [PubMed: 30363578]

125. Foster NL et al. Peripheral beta-adrenergic blockade treatment of parkinsonian tremor. Ann. Neurol 16, 505–508 (1984). [PubMed: 6149724]

126. Connolly BS & Lang AE Pharmacological treatment of Parkinson disease: a review. JAMA 311, 1670–1683 (2014). [PubMed: 24756517]

127. Snijders AH et al. Physiology of freezing of gait. Ann. Neurol 80, 644–659 (2016). [PubMed: 27649270]

128. Henderson EJ et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 15, 249–258 (2016). [PubMed: 26795874]

129. Chung KA, Lobb BM, Nutt JG & Horak FB Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. Neurology 75, 1263–1269 (2010). [PubMed: 20810998]

130. Moreau C et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. Lancet Neurol. 11, 589–596 (2012). [PubMed: 22658702]

131. Ahlskog JE & Muenter MD Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov. Disord 16, 448–458 (2001). [PubMed: 11391738]

132. Hodgson RA et al. Preladenant, a selective A2Areceptor antagonist, is active in primate models of movement disorders. Exp. Neurol 225, 384–390 (2010). [PubMed: 20655910]

133. Hauser R et al. Phase-3 clinical trials of adjunctive therapy with preladenant, an adenosine 2a antagonist, in patients with Parkinson's disease [abstract]. Neurology 82 (Suppl. 10), P7.087 (2014).

134. Hauser RA et al. Preladenant as an adjunctive therapy with levodopa in Parkinson disease: two randomized clinical trials and lessons learned. JAMA Neurol. 72, 1491–1500 (2015). [PubMed: 26523919]

135. Stocchi F et al. Randomized trial of preladenant, given as monotherapy, in patients with early Parkinson disease. Neurology 88, 2198–2206 (2017). [PubMed: 28490648]

136. Fernandez HH et al. Istradefylline as monotherapy for Parkinson disease: results of the 6002-US-051 trial. Parkonsonism Relat. Disord 16, 16–20 (2010).

137. LeWitt PA et al. Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces off time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). Ann. Neurol 63, 295–302 (2008). [PubMed: 18306243]

138. Hauser RA et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. Mov. Disord 23, 2177–2185 (2008). [PubMed: 18831530]

139. Sako W, Murakami N, Motohama K, Izumi Y & Kaji R The effect of istradefylline for Parkinson's disease: a meta-analysis. Sci. Rep 7, 18018 (2017). [PubMed: 29269791]

140. Carta M, Carlsson T, Muñoz A, Kirik D & Björklund A Role of serotonin neurons in the induction of levodopa- and graft-induced dyskinesias in Parkinson's disease. Mov. Disord 25, S174–179 (2010). [PubMed: 20187238]

141. Bibbiani F, Oh JD & Chase TN Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models. Neurology 57, 1829–1834 (2001). [PubMed: 11723272]

142. Luginger E, Wenning G, Bösch S & Poewe W Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. Mov. Disord 15, 873–878 (2000). [PubMed: 11009193]

143. Picconi B, Hernández LF, Obeso JA & Calabresi P Motor complications in Parkinson's disease: striatal molecular and electrophysiological mechanisms of dyskinesias. Mov. Disord 33, 867–876 (2018). [PubMed: 29219207]

144. Lentz TB, Gray SJ & Samulski RJ Viral vectors for gene delivery to the central nervous system. Neurobiol. Dis 48, 179–188 (2012). [PubMed: 22001604]

145. Eberling JL et al. Results from a phase I safety trial of hAADC gene therapy for Parkinson disease. Neurology 70, 1980–1983 (2008). [PubMed: 18401019]

146. LeWitt PA et al. AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham- surgery controlled, randomised trial. Lancet Neurol. 10, 309–319 (2011). [PubMed: 21419704]

147. Christine CW et al. Safety and tolerability of putaminal AADC gene therapy for Parkinson disease. Neurology 73, 1662–1669 (2009). [PubMed: 19828868]

148. Sánchez-Pernaute R, Harvey-White J, Cunningham J & Bankiewicz KS Functional effect of adeno-associated virus mediated gene transfer of aromatic L-amino acid decarboxylase into the striatum of 6-OHDA-lesioned rats. Mol. Ther 4, 324–330 (2001). [PubMed: 11592835]

149. Fan D-S et al. Behavioral recovery in 6-hydroxydopamine-lesioned rats by cotransduction of striatum with tyrosine hydroxylase and aromatic- amino acid decarboxylase genes using two separate adeno-associated virus vectors. Hum. Gene Ther 9, 2527–2535 (1998). [PubMed: 9853519]

150. Christine CW et al. VY-AADC01 in medically refractory Parkinson's disease: safety and efficacy of a phase 1b dose-ranging study 12 months and beyond [abstract]. Ann. Neurol 84, S1–S280 (2018).

151. Emborg ME et al. Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism. J. Cereb. Blood Flow Metab 27, 501–509 (2007). [PubMed: 16835631]

152. Niethammer M et al. Long-term follow-up of a randomized AAV2- GAD gene therapy trial for Parkinson's disease. JCI Insight 2, e90133 (2017). [PubMed: 28405611]

153. Rosenblad C Protection and regeneration of nigral dopaminergic neurons by neurturin or GDNF in a partial lesion model of Parkinson's disease after administration into the striatum or the lateral ventricle. Eur. J. Neurosci 11, 1554–1566 (1999). [PubMed: 10215908]

154. Rosenblad C, Kirik D & Bjorklund A Neurturin enhances the survival of intrastriatal fetal dopaminergic transplants. Neuroreport 10, 1783–1787 (1999). [PubMed: 10501575]

155. Lin LFH, Doherty DH, Lile JD, Bektesh S & Collins F GDNF: a glial cell line - derived neurotrophic factor for midbrain dopaminergic neurons. Science 260, 1130–1132 (1993). [PubMed: 8493557]

156. Miyoshi Y et al. Glial cell line-derived neurotrophic factor-levodopa interactions and reduction of side effects in parkinsonian monkeys. Ann. Neurol 42, 208–214 (1997). [PubMed: 9266731]

157. Zhang Z et al. Dose response to intraventricular glial cell line-derived neurotrophic factor administration in parkinsonian monkeys. J. Pharmacol. Exp. Ther 282, 1396–1401 (1997). [PubMed: 9316852]

158. Kotzbauer PT et al. Neurturin, a relative of glial- cell-line-derived neurotrophic factor. Nature 384, 467–470 (1996). [PubMed: 8945474]

159. Gasmi M et al. AAV2-mediated delivery of human neurturin to the rat nigrostriatal system: Long-term efficacy and tolerability of CERE-120 for Parkinson's disease. Neurobiol. Dis 27, 67–76 (2007). [PubMed: 17532642]

160. Herzog CD et al. Striatal delivery of CERE-120, an AAV2 vector encoding human neurturin, enhances activity of the dopaminergic nigrostriatal system in aged monkeys. Mov. Disord 22, 1124–1132 (2007). [PubMed: 17443702]

161. Kordower JH et al. Delivery of neurturin by AAV2 (CERE-120)-mediated gene transfer provides structural and functional neuroprotection and neurorestoration in MPTP-treated monkeys. Ann. Neurol 60, 706–715 (2006). [PubMed: 17192932]

162. Marks WJ et al. Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. Lancet Neurol. 7, 400–408 (2008). [PubMed: 18387850]
163. Marks WJ et al. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neurol 9, 1164–1172 (2010). [PubMed: 20970382]
164. Lindholm P et al. Novel neurotrophic factor CDNF protects and rescues midbrain dopamine neurons in vivo. Nature 448, 73–77 (2007). [PubMed: 17611540]
165. Tsukahara T, Takeda M, Shimohama S, Ohara O & Hashimoto N Effects of brain-derived neurotrophic factor on 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine-induced parkinsonism in monkeys. Neurosurgery 37, 733–741 (1995). [PubMed: 8559303]
166. Yasuhara T et al. Neuroprotective effects of vascular endothelial growth factor (VEGF) upon dopaminergic neurons in a rat model of Parkinson's disease. Eur. J. Neurosci 19, 1494–1504 (2004). [PubMed: 15066146]
167. Barker RA, Drouin-Ouellet J & Parmar M Cell-based therapies for Parkinson disease-past insights and future potential. Nat. Rev. Neurol 11, 492–503 (2015). [PubMed: 26240036]
168. Barker RA, Barrett J, Mason SL & Björklund A. Fetal dopaminergic transplantation trials and the future of neural grafting in Parkinson's disease. Lancet Neurol. 12, 85–91 (2013).
169. Lindvall O et al. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 247, 574–577 (1990). [PubMed: 2105529]
170. Ma Y et al. Dyskinesia after fetal cell transplantation for parkinsonism: a PET study. Ann. Neurol 52, 628–634 (2002). [PubMed: 12402261]
171. Freed CR et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N. Engl. J. Med 344, 710–719 (2001). [PubMed: 11236774]
172. Olanow CW et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann. Neurol 54, 403–414 (2003). [PubMed: 12953276]
173. Roy NS et al. Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes. Nat. Med 12, 1259–1268 (2006). [PubMed: 17057709]
174. Kriks S et al. Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease. Nature 480, 547–551 (2011). [PubMed: 22056989]
175. Grealish S et al. Human ESC-derived dopamine neurons show similar preclinical efficacy and potency to fetal neurons when grafted in a rat model of Parkinson's disease. Cell Stem Cell 15, 653–665 (2014). [PubMed: 25517469]
176. Takahashi K & Yamanaka S Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126, 663–676 (2006). [PubMed: 16904174]
177. Kikuchi T et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. Nature 548, 592–596 (2017). [PubMed: 28858313]
178. Barker RA, Parmar M, Studer L & Takahashi J Human trials of stem cell-derived dopamine neurons for Parkinson's disease: dawn of a new era. Cell Stem Cell 21, 569–573 (2017). [PubMed: 29100010]
179. US National Library of Medicine. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT03119636 (2017).
180. Okun MS Deep-brain stimulation — entering the era of human neural-network modulation. N. Engl. J. Med 371, 1369–1373 (2014). [PubMed: 25197963]
181. Williams A et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol 9, 581–591 (2010). [PubMed: 20434403]
182. Weaver FM et al. Bilateral deep brain stimulation versus best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 301, 63–73 (2009). [PubMed: 19126811]
183. Okun MS et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. Ann. Neurol 65, 586–595 (2009). [PubMed: 19288469]

184. Deuschl G et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N. Engl. J. Med 355, 896–908 (2006). [PubMed: 16943402]

185. Follett KA et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N. Engl. J. Med 362, 2077–2091 (2010). [PubMed: 20519680]

186. Grabli D et al. Gait disorders in parkinsonian monkeys with pedunculopontine nucleus lesions: a tale of two systems. J. Neurosci 33, 11986–11993 (2013). [PubMed: 23864685]

187. Hickey P & Stacy M Deep brain stimulation: a paradigm shifting approach to treat Parkinson's disease. Front. Neurosci 10, 173 (2016). [PubMed: 27199637]

188. Jenkinson N, Nandi D, Miall RC, Stein JF & Aziz TZ Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey. Neuroreport 15, 2621–2624 (2004). [PubMed: 15570164]

189. Stefani A et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 130, 1596–1607 (2007). [PubMed: 17251240]

190. Plaha P & Gill SS Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease. Neuroreport 16, 1883–1887 (2005). [PubMed: 16272872]

191. Chastan N et al. Effects of nigral stimulation on locomotion and postural stability in patients with Parkinson's disease. Brain 132, 172–184 (2009). [PubMed: 19001482]

192. Weiss D et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. Brain 136, 2098–2108 (2013). [PubMed: 23757762]

193. Quinn EJ et al. Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. Mov. Disord 30, 1750–1758 (2015). [PubMed: 26360123]

194. Grossman N et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell 169, 1029–1041 (2017). [PubMed: 28575667]

195. Gittis A Probing new targets for movement disorders. Science 361, 462 (2018). [PubMed: 30072532]

196. Chen S et al. Near-infrared deep brain stimulation via upconversion nanoparticle–mediated optogenetics. Science 359, 679–684 (2018). [PubMed: 29439241]

197. Fischer DL et al. Subthalamic nucleus deep brain stimulation does not modify the functional deficits or axonopathy induced by nigrostriatal α-synuclein overexpression. Sci. Rep 7, 16356 (2017). [PubMed: 29180681]

198. van Horne CG et al. Implantation of autologous peripheral nerve grafts into the substantia nigra of subjects with idiopathic Parkinson's disease treated with bilateral STN DBS: a report of safety and feasibility. J. Neurosurg 126, 1140–1147 (2017). [PubMed: 27153166]

199. Braak H et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211 (2003). [PubMed: 12498954]

200. Mortiboys H, Aasly J & Bandmann O Ursocholanic acid rescues mitochondrial function in common forms of familial Parkinson's disease. Brain 136, 3038–3050 (2013). [PubMed: 24000005]

201. Park J et al. Mitochondrial dysfunction in *Drosophila* PINK1 mutants is complemented by parkin. Nature 441, 1157–1161 (2006). [PubMed: 16672980]

202. Tain LS et al. Rapamycin activation of 4E-BP prevents parkinsonian dopaminergic neuron loss. Nat. Neurosci 12, 1129–1135 (2009). [PubMed: 19684592]

203. Clark IE et al. *Drosophila* pink1 is required for mitochondrial function and interacts genetically with parkin. Nature 441, 1162–1166 (2006). [PubMed: 16672981]

204. Pickrell AM & Youle RJ The roles of PINK1, Parkin, and mitochondrial fidelity in parkinson's disease. Neuron 85, 257–273 (2015). [PubMed: 25611507]

205. Shin JH et al. PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in parkinson's disease. Cell 144, 689–702 (2011). [PubMed: 21376232]

206. Ottolini D, Calì T, Negro A & Brini M The Parkinson disease-related protein DJ-1 counteracts mitochondrial impairment induced by the tumour suppressor protein p53 by enhancing endoplasmic reticulum-mitochondria tethering. Hum. Mol. Genet 22, 2152–2168 (2013). [PubMed: 23418303]

207. Feng CW et al. Neuroprotective effect of the marine-derived compound 11-dehydrosinulariolide through DJ-1-related pathway in in vitro and in vivo models of Parkinson's disease. Mar. Drugs 14, E187 (2016). [PubMed: 27763504]
208. Ablat N et al. Neuroprotective effects of a standardized flavonoid extract from safflower against a rotenone- induced rat model of Parkinson's disease. Molecules 21, E1107 (2016). [PubMed: 27563865]
209. Zavodszky E et al. Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy. Nat. Commun 5, 3828 (2014). [PubMed: 24819384]
210. Temkin P et al. The retromer supports AMPA receptor trafficking during LTP. Neuron 94, 74–82 (2017). [PubMed: 28384478]
211. Kim S et al. GBA1 deficiency negatively affects physiological α-synuclein tetramers and related multimers. Proc. Natl Acad. Sci. USA 115, 798–803 (2018). [PubMed: 29311330]
212. Shults CW et al. Effects of coenzyme Q 10 in early Parkinson disease: evidence of slowing of the functional decline. Arch. Neurol 59, 1541–1550 (2002). [PubMed: 12374491]
213. Beal MF et al. A randomized clinical trial of high- dosage coenzyme Q10 in early parkinson disease no evidence of benefit. JAMA Neurol. 75, 543–552 (2014).
214. Poulter MO, Payne KB & Steiner JP Neuroimmunophilins: a novel drug therapy for the reversal of neurodegenerative disease? Neuroscience 128, 1–6 (2004). [PubMed: 15450348]
215. Kieburtz K et al. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. Neurology 68, 20–28 (2007). [PubMed: 17200487]
216. Mischley LK, Lau RC, Shankland EG, Wilbur TK & Padowski JM Phase IIb study of intranasal glutathione in Parkinson's disease. J. Parkinsons Dis 7, 289–299 (2017). [PubMed: 28436395]
217. Monti DA et al. N-Acetyl cysteine may support dopamine neurons in Parkinson's disease: preliminary clinical and cell line data. PLOS ONE 11, e0157602 (2016). [PubMed: 27309537]
218. Lin K. Der et al. Statin therapy prevents the onset of Parkinson disease in patients with diabetes. Ann. Neurol 80, 532–540 (2016). [PubMed: 27471847]
219. Liu G et al. Statins may facilitate Parkinson's disease: insight gained from a large, national claims database. Mov. Disord 32, 913–917 (2017). [PubMed: 28370314]
220. Ravina B et al. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology 66, 664–671 (2006). [PubMed: 16481597]
221. Jin H et al. Mitochondria-targeted antioxidants for treatment of Parkinson's disease: preclinical and clinical outcomes. Biochim. Biophys. Acta 1842, 1282–1294 (2014). [PubMed: 24060637]
222. Snow BJ et al. A double-blind, placebo-controlled study to assess the mitochondria- targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease. Mov. Disord 25, 1670–1674 (2010). [PubMed: 20568096]
223. Bido S, Soria FN, Fan RZ, Bezard E & Tieu K Mitochondrial division inhibitor-1 is neuroprotective in the A53T-α-synuclein rat model of Parkinson's disease. Sci. Rep 7, 7495 (2017). [PubMed: 28790323]
224. Shaltouki A, Hsieh CH, Kim MJ & Wang X Alpha-synuclein delays mitophagy and targeting Miro rescues neuron loss in Parkinson's models. Acta Neuropathol. 136, 607–620 (2018). [PubMed: 29923074]
225. Di Paolo T et al. AQW051, a novel and selective nicotinic acetylcholine receptor α7 partial agonist, reduces l-Dopa-induced dyskinesias and extends the duration of l-Dopa effects in parkinsonian monkeys. Parkinsonism Relat. Disord 20, 1119–1123 (2014). [PubMed: 25172125]
226. Tison F et al. A phase 2A trial of the novel mGluR5- negative allosteric modulator dipraglurant for levodopa-induced dyskinesia in Parkinson's disease. Mov. Disord 31, 1373–1380 (2016). [PubMed: 27214664]
227. Muramatsu SI et al. A phase i study of aromatic l-amino acid decarboxylase gene therapy for parkinson's disease. Mol. Ther 18, 1731–1735 (2010). [PubMed: 20606642]
228. Mittermeyer G et al. Long-term evaluation of a phase 1 study of AADC gene therapy for Parkinson's disease. Hum. Gene Ther 23, 377–381 (2012). [PubMed: 22424171]

229. Palfi S et al. Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease: a dose escalation, open- label, phase 1/2 trial. Lancet 383, 1138–1146 (2014). [PubMed: 24412048]

230. Kaplitt MG et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet 369, 2097–2105 (2007). [PubMed: 17586305]

231. Gill SS et al. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat. Med 9, 589–595 (2003). [PubMed: 12669033]

232. Slevin JT et al. Improvement of bilateral motor functions in patients with Parkinson disease through the unilateral intraputaminal infusion of glial cell line—derived neurotrophic factor. J. Neurosurg 102, 216–222 (2005). [PubMed: 15739547]

233. Lang AE et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Ann. Neurol 59, 459–466 (2006). [PubMed: 16429411]

234. Patel NK et al. Intraputamenal infusion of glial cell line-derived neurotrophic factor in PD: A two-year outcome study. Ann. Neurol 57, 298–302 (2005). [PubMed: 15668979]

235. Study Group TG. Randomized Parkinson's trial of GDNF administered via intermittent intraputamenal convection-enhanced delivery [abstract]. Mov. Disord 32 (Suppl. 2), 1420 (2017).

236. Bartus RT et al. Safety/feasibility of targeting the substantia nigra with AAV2-neurturin in Parkinson patients. Neurology 80, 1698–1701 (2013). [PubMed: 23576625]

237. Warren Olanow C et al. Gene delivery of neurturin to putamen and substantia nigra in Parkinson disease: a double-blind, randomized, controlled trial. Ann. Neurol 78, 248–257 (2015). [PubMed: 26061140]

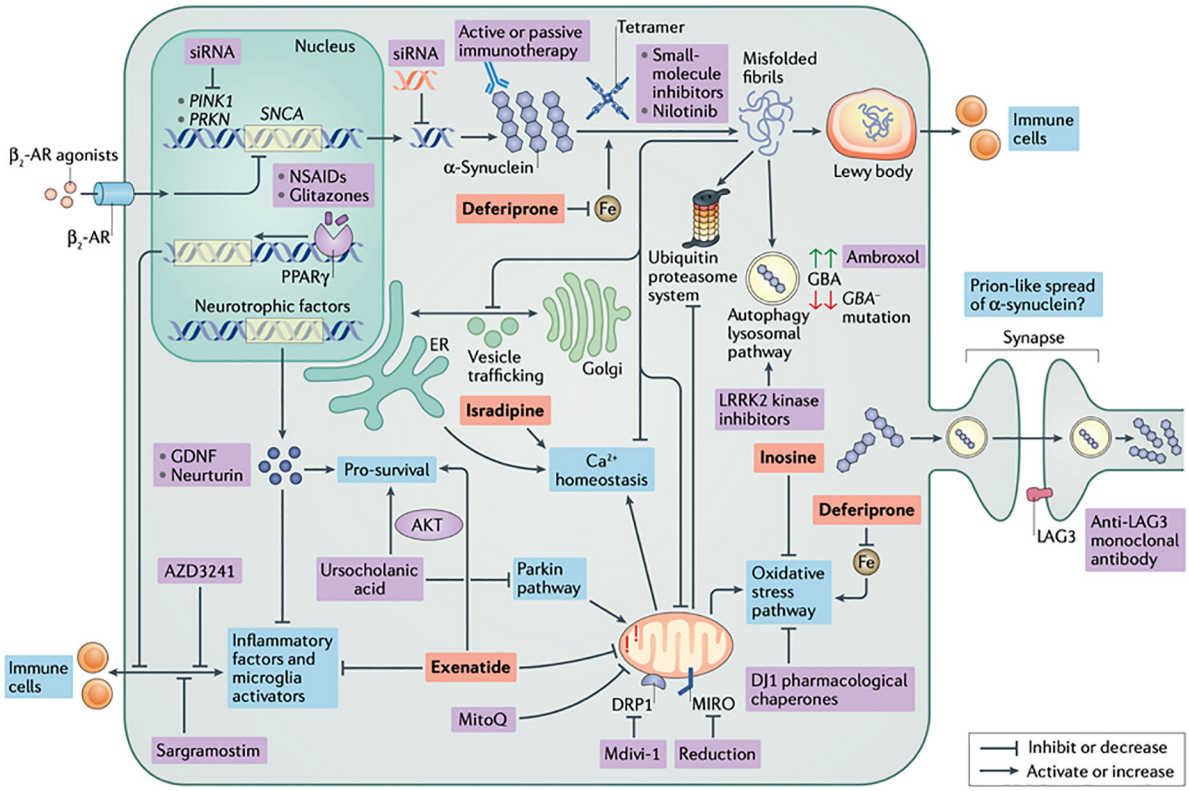

Fig. 1 |. Mechanisms of potential therapies for Parkinson disease.

Numerous potential therapies for Parkinson disease (PD) are at various stages of preclinical and clinical testing. These agents target many aspects of PD pathogenesis. Therapies in bold are at advanced stages of testing. Several basic pathophysiological pathways are depicted, including those that lead to Lewy bodies, and those involving inflammatory factors, mitochondrial dysfunction and oxidative stress. A synapse to the right illustrates the potential spread of pathological α-synuclein to nearby cells. Bars indicate either inhibition or decrease and arrows indicate activation or increase. Arrows are also used for a sequence of events in a pathway. The exclamation marks inside the mitochondrion represent a dysfunctional mitochondrion. AKT, protein kinase B; β2-AR, β2-adrenergic receptor; DJ1, protein deglycase DJ1; DRP1, dynamin-1-like protein; ER, endoplasmic reticulum; GBA, glucocerebrosidase; GDNF, glial cell-derived neurotrophic factor; LAG3, lymphocyte-activation gene 3; LRRK2, leucine- rich repeat kinase 2; Mdivi-1, mitochondrial division inhibitor 1; MIRO, mitochondrial Rho GTPase 1; MitoQ, mitoquinone; PINK1, PTEN-induced kinase 1; PPARγ, peroxisome proliferator-activated receptor-γ; siRNA, small interfering RNA.

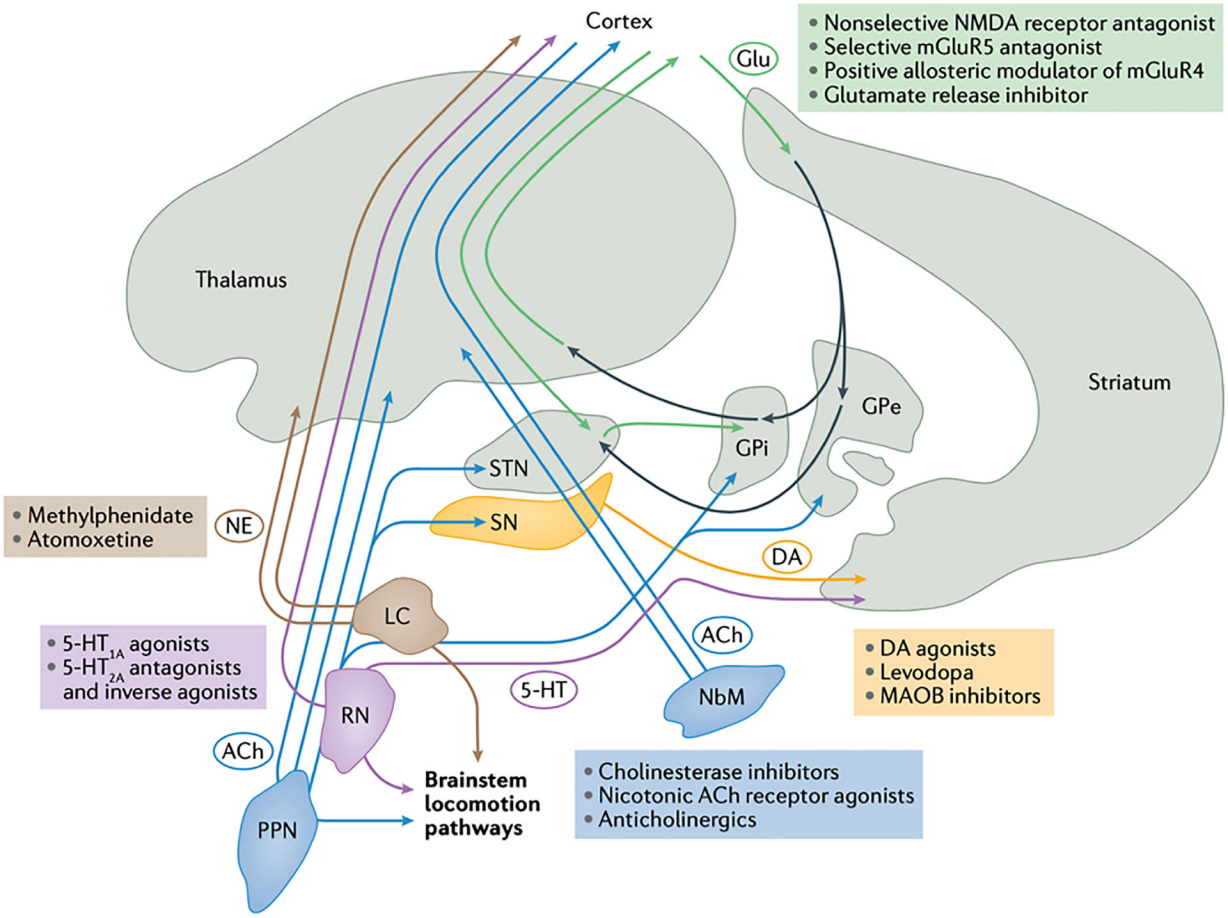

Fig. 2 |. Basal ganglia neurotransmitter network.

A classic model of the basal ganglia is shown with a striatonigral direct pathway through the globus pallidus internus (GPi), an indirect pathway reaching the globus pallidus externus (GPe) and subthalamic nucleus (STN) before the GPi and a hyperdirect pathway to the STN. Dopaminergic input to the striatum is supplied by the substantia nigra (SN). Other neurotransmitter foci are also depicted, including the pedunculopontine nucleus (PPN) and nucleus basalis of Meynert (NbM) for acetylcholine (ACh), the raphe nucleus (RN) for serotonin (5-hydroxytryptamine (5-HT)) and the locus coeruleus (LC) for noradrenaline (NE). These neurotransmitters travel throughout the basal ganglia and related structures and play an important part in Parkinson disease motor symptoms. Several existing and investigational therapies that aim to address abnormal levels of neurotransmitters are shown. DA, dopamine; mGluR, metabotropic glutamate receptor; NMDA, *N*-methyl-d-aspartate.

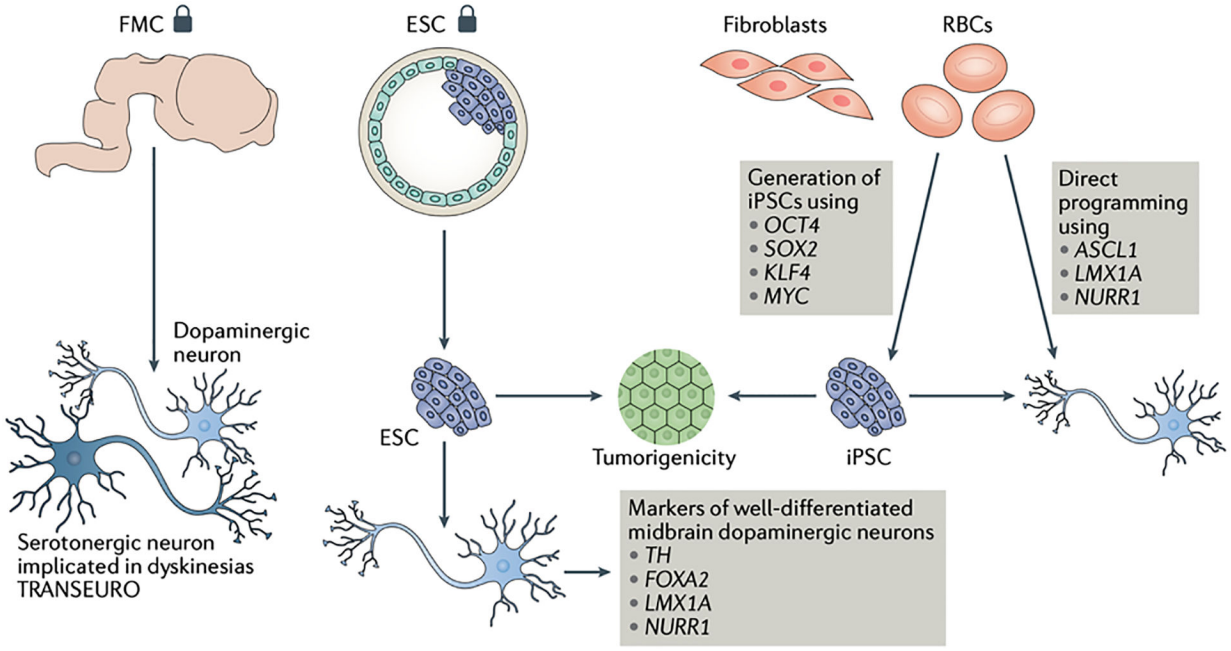

Fig. 3 |. Extraction and induction of dopaminergic cells for neuronal restoration.

There are several emerging approaches for extracting dopaminergic cells. Fetal mesencephalic cell (FMC) transplantation initially seemed promising, but runaway dyskinesias halted further trials. The TRANSEURO consortium will comprehensively re-evaluate this therapy. Embryonic stem cells (ESCs) can be used for transplantation but carry the same ethical challenges as FMCs (the ethical challenge is visually depicted by the locks in the figure). Red blood cell (RBC) and fibroblast induced pluripotent stem cells (iPSCs) are an alternative approach that eliminates this ethical challenge, but, similar to other pluripotent stem cells, these cells carry neoplastic potential. Finally, neurons induced by direct programming from somatic cells might be a viable but technically challenging route. The figure depicts some transcription factors used in reprogramming cells. *ASCL1*, achaete–scute homologue 1; *FOXA2*, hepatocyte nuclear factor 3β; *KLF4*, Krüppel-like factor 4; *LMX1A*, LIM homeobox transcription factor 1α; *MYC*, Myc proto-oncogene protein; *NURR1*, nuclear receptor related-1 protein; *OCT4*, organic cation/carnitine transporter 4; *SOX2*, transcription factor SOX2; *TH*, tyrosine 3-monooxygenase.

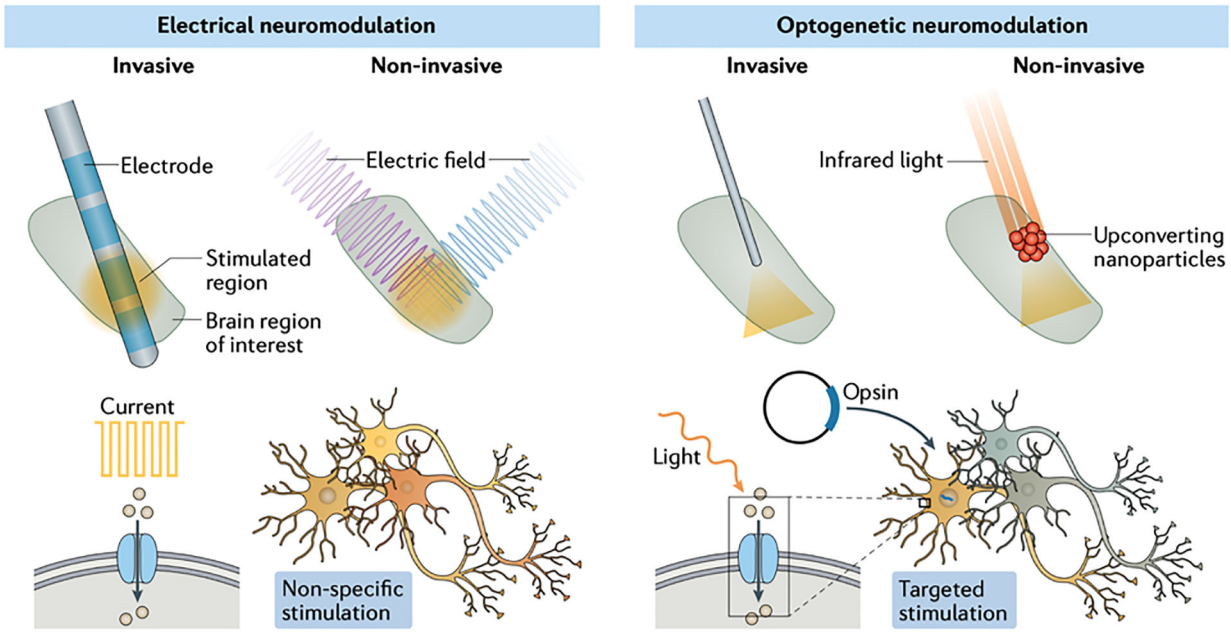

Fig. 4 |. Neuromodulation.

Deep brain stimulation is an established therapy for Parkinson disease, but there is growing interest in non-invasive electrical stimulation modalities and optogenetic stimulation modalities. Non-invasive electrical stimulation might be achieved with interference of two electric fields with slightly different frequencies (temporal interference), leading to localized stimulation. In optogenetic stimulation, an opsin is delivered to specific neurons that then express a light-sensitive channel on their membrane, permitting their stimulation with direct light source. Alternatively, certain nanoparticles, if delivered inside the brain, are able to convert infrared light from an extracranial source to visible light in the brain and hence permit the non-invasive stimulation of optogenetically modified neurons. Electrical stimulation approaches are generally non-specific, whereas optogenetic approaches have the potential for targeting specific neurons.

Table 1 |

Mutations and pathways implicated in PD and targeted therapies under development

Gene (inheritance)	Disease entity	Mechanism of pathology in mutation	Targeted therapy (in the pipeline and in clinical trials)
SNCA (autosomal dominant)	PARK1	• Encodes α-synuclein • Toxic oligomers of α-synuclein cause organelle dysfunction and impair interorganelle contacts, autophagy and synaptic vesicle trafficking[14–18] • Potential prion-like spread of α-synuclein oligomers[199]	• Immunotherapies • Strategies to decrease production, inhibit misfolding and enhance clearance of α-synuclein
LRRK2 (autosomal dominant)	PARK8	• Encodes leucine-rich repeat kinase 2 • Increases kinase activity in neurons and promotes cell death[55] • Mitochondrial DNA dysfunction • Increases inflammatory response and apoptosis	• Ursocholanic acid[200] • Ursodeoxycholic acid • LRRK2 small-molecule kinase inhibitors[51]
PINK1 (autosomal recessive)	PARK6	• Encodes PTEN-induced kinase 1 • Mitochondrial dysfunction and mitochondrial calcium mishandling[201]	• Ursocholanic acid[200] • Ursodeoxycholic acid • Rapamycin[202] • Mitochondrial rescue therapies • Silencing by siRNAs (tested in cultured neurons)
PRKN (autosomal recessive)	PARK2	• Encodes parkin • Dysregulation in mitophagy (in concordance with PINK1)[203,204] • Work in *Drosophila* suggests that parkin and PINK1 might function in a common genetic pathway and play a role in mitochondrial quality control and mitophagy[203] • Increases expression of PARIS and consequently represses PGC1α[205]	
PARK7 (autosomal recessive)	PARK7	• Encodes protein deglycase DJ1 • Increases sensitivity of neurons towards oxidative stress • DJ1 might contribute to the endoplasmic reticulum–mitochondria tethering, and reduced levels cause mitochondrial fragmentation and mitochondrial calcium mishandling[206]	• Small-molecule chaperones that specifically bind to DJ1 are in the pipeline • Phenylbutyrate upregulates *DJ1* gene expression • 11-Dehydrosinulariolide (neuroprotective effect in vitro and in vivo in animal models)[207] • Flavonoid extract[208]
VPS35 (autosomal dominant)	PARK17	• Encodes vacuolar protein sorting-associated protein 35 • Respiratory defects in complex I and II • Increases mitochondrial fragmentation through increased interaction with DLP1 (ref.[111]) • Impairs WASH complex and resulting macroautophagy[209] • AMPA receptor trafficking defects[210]	• siRNA • Mitochondrial rescue therapies

Gene (inheritance)	Disease entity	Mechanism of pathology in mutation	Targeted therapy (in the pipeline and in clinical trials)
GBA (autosomal recessive)	PARK18	• Encodes glucocerebrosidase • Inhibition of macroautophagy and chaperone-mediated autophagy • Decreases proportion of α-synuclein tetramers and related multimers compared with monomers[47,69,211]	• Modulation of glucosylceramidase activity with ambroxol (AiM-PD trial; NCT02941822), LTI-291 or AT3375 • Glucosylceramide synthase inhibitors: GZ/SAR402671 (MOVES-PD trial; NCT02906020)

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; DLP1, dynamin-1-like protein; PARIS; parkin-interacting substrate; PD, Parkinson disease; PGC1α, peroxisome proliferator-activated receptor-γ co-activator 1α; siRNA, short interfering RNA.

Table 2 |

α-Synuclein-targeting therapies in clinical trials and potential future targets and methods

Stage	Inhibition of α-synuclein production	Inhibition of misfolding or aggregation of α-synuclein	Activation of cellular turnover of α-synuclein	Immunotherapies
In clinical trials	None	• Misfolding: NPT200–11 (completed phase I) • Aggregation: NPT088 (completed phase I in patients with AD and will be tested in PD on the basis of AD study results); glycerol phenylbutyrate (phase I); nilotinib (phase II); PBT434 (phase I)	In patients with PD carrying a *GBA* mutation: ambroxol (phase II); GZ/SAR40261 (phase II; MOVES-PD)	• Passive immunization: RO7046015, also known as PRX002 (PASADENA; phase II); BIIB054 (SPARK; phase II); MEDI1341 (phase I); BAN0805 (expected to start phase I in 2019) • Active immunization: affitope PD01 (completed phase I); affitope PD03 (completed phase I)
Future targets or methods	• siRNAs • ASO • β_2-AR agonists	Small-molecule inhibitors: squalamine; epigallocatechin gallate anle138b; CLR01; KYP-2047 (prolyl oligopeptidase inhibitor)	IU1 (small molecule)	LAG3 (anti-LAG3 monoclonal antibody BMS-986016 is in early clinical trial phases for patients with cancer and can be tested in PD if deemed safe)

β_2-AR, β_2-adrenergic receptor; AD, Alzheimer disease; ASO, antisense oligonucleotide; IU1, 1-[1-(4-fluorophenyl)-2,5-dimethylpyrrol- 3-yl]-2-pyrrolidin-1-ylethanone; LAG3, lymphocyte-activation gene 3; PD, Parkinson disease; siRNA, small interfering RNA.

Table 3 |

Neuronal mitochondria rescue strategies

Agents	Initial study results	Current clinical trials and future directions
Therapies targeting the mitochondrial oxidative stress pathway		
Coenzyme Q10 (CoQ10) and GPI 1485	• CoQ10 is an antioxidant that supports mitochondrial function. CoQ10 was found to be safe and well tolerated in phase I trials and had possible clinical benefit in a phase II trial (QE2 study)[212]. The QE3 study, which used a higher dosage of CoQ10, was a randomized, double-blinded phase III study that failed to reveal disease-modification potential for CoQ10 (ref.[213]) • GPI 1485 is a neurotrophic immunophilin-ligand that was shown to reverse neuronal degeneration and prevents cell death in animal models. In a 6-month phase II clinical trial of GPI 1485, there was a trend towards favourable impact on imaging but not clinical measures in patients with PD[214] • The NINDS NET-PD trial, which enrolled and randomly assigned 213 participants, 71 to the CoQ10, 71 to the GPI 1485 and 71 to the placebo arm, was not conclusive regarding the disease-modifying effects of the tested compounds and recommended that further studies should be done to confirm efficacy[215]	• CoQ10 trials failed to reveal disease-modification potential for PD; therefore, no further clinical trials are planned • Multiple antioxidants failed in disease-modification trials in the past owing to a multitude of factors, including patient selection, bias from additional therapies, lack of a reliable biomarker and poorly defined patient selection and outcomes
Glutathione	• Reduced glutathione was found early in the course of PD, and glutathione augmentation has been proposed as a therapeutic strategy in PD • In a phase IIb study, intranasal glutathione was not superior to placebo[216]	Glutathione/NAC or EPI-589: safety and biomarker study in PD (NCT02462603)
N-Acetylcysteine (NAC)	NAC may restore the level of glutathione in neurons by functioning as a source of cysteine; hence, NAC has the potential to lower oxidative stress. Some data suggest a positive impact of NAC on dopaminergic neurons[217]	NAC for Neuroprotection in PD (NAC for PD) (NCT01470027)
Inosine	Inosine increases levels of urate, a potential antioxidant, and was proved safe and tolerable in patients with early PD (SURE-PD trial)[118]	SURE-PD III is in progress and plans to enrol 270 patients with early untreated PD
Statins	Different studies reported increased and decreased risk of PD with use of statins[218,219]: in Taiwanese patients with diabetes mellitus, statin use was associated with reduced risk of PD whereas a retrospective case–control analysis conducted in the USA suggested increased odds	Whether statins increase, decrease or have no effect on the risk of PD remains a controversial issue; larger multicentre trials are needed to confirm the findings
Glitazones	• The use of glitazones has been associated with a decreased risk of incident PD in populations with diabetes • The NET-PD FS zone investigators found that pioglitazone did not modify progression of PD[114]	• Although pioglitazone was deemed futile, other glitazones are yet to be evaluated for their disease-modification potential in PD • Larger trials with careful patient selection and better-defined primary outcomes are needed
Minocycline and creatine	• Both minocycline and creatine have been shown to protect against MPTP-induced dopamine depletion in mice • The NINDS NET-PD investigators found that neither agent was futile in phase II trials, but larger efficacy trials are needed[220]	Combination therapies using multiple antioxidants with better-defined inclusion criteria and outcome measured are being planned

Agents	Initial study results	Current clinical trials and future directions
Mitochondria-specific therapies		
Mitochondria-targeted antioxidant therapy	• Examples include MitoQ, MitoVitE, MitoApocynin and MitoTEMPOL[221] • Evidence of neuroprotective effects from animal models • These conjugated compounds are postulated to bind to the mitochondria more easily than the parent antioxidant[221] • MitoQ did not slow progression of PD in a double-blinded, placebo-controlled trial[222]	• Conjugated compounds other than MitoQ have yet to be tested for disease-modification potential in clinical trials • Failures of parent and conjugated antioxidant compounds to slow disease progression in PD raise questions about the role of the oxidative stress pathway in PD
Dynamin-1-like protein (DRP1)-targeting compounds	Mdivi-1 (mitochondrial division inhibitor) is a DRP1 inhibitor that has been shown to block the excessive mitochondrial fission implicated in PD pathogenesis[223]	• No clinical trials of DRP-targeting compounds and MIRO are planned • Safety issues remain a concern and extensive testing in preclinical model is recommended prior to clinical application
Mitochondrial Rho GTPase 1 (MIRO)	• MIRO is implicated in mitochondrial motility and abnormally accumulates on the mitochondrial surface, leading to delayed mitophagy • Partial reduction of MIRO rescues mitophagy[224]	

MitoVitE, mitotocopherol; MitoQ, mitoquinone; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NINDS, US National Institute of Neurological Disorders and Stroke; PD, Parkinson disease.

Table 4 |

Major non-dopaminergic neurotransmitter networks in current and future PD motor treatment

Neurotransmitter	Target and/or receptor	Medications	Effect on motor symptoms	Clinical trials updates	Future challeng
Acetylcholine	• Cholinesterase inhibitors: affect balance and gait circuitry in mesencephalic locomotor region (that is, cholinergic pedunculopontine nucleus) • Anticholinergics act on muscarinic receptors	• Cholinesterase inhibitors: donepezil and rivastigmine • Nicotinic acetylcholine receptor-α7 agonist: AQW051 • Anticholinergics such as trihexyphenidyl	• Cholinesterase inhibitors might improve gait and reduce falls in patients with PD • Nicotinic acetylcholine receptor-α7 agonist was hypothesized to improve duration of action of levodopa and decrease LID on the basis of MPTP-lesioned monkeys[225] • Anticholinergics have a limited role in controlling parkinsonian tremor	• Effect of donepezil on gait and balance in PD (NCT02206620): ongoing • AQW051 did not improve dyskinesias or parkinsonian severity in a phase II clinical trial (NCT01474421)	•
Adenosine	Adenosine (A_{2A}) receptor antagonist	• Istradefylline • Preladenant • Tozadenant	• Reduction of 'off' time when added to levodopa • Possible role for treating postural abnormalities	• Istradefylline proved efficient in reducing motor fluctuations in randomized trials • Preladenant was deemed futile in three phase III trials (NCT01155479) • Tozadenant trial terminated after reports of agranulocytosis (NCT03051607)	•
Serotonin	Variable effects, mostly on 5-HT_{1A} and 5-HT_{2A}	• 5-HT1A agonists: buspirone, eltoprazine, sarizotan and NLX-112 • 5-HT_{2A} antagonists and inverse agonists • Clozapine	• Improve dyskinesias (5-HT_{1A} agonists) • Helps rest tremor (clozapine)	• Buspirone for LID: seems to be more effective in milder cases of LID • Eltoprazine reduced peak-dose dyskinesia in a phase IIa study • Sarizotan: improved dyskinesias but worsened motor	•

Neurotransmitter	Target and/or receptor	Medications	Effect on motor symptoms	Clinical trials updates	Future challeng
				• symptoms in a phase III study • NLX-112: no clinical trial results available yet, but effective at reducing LID in parkinsonian rats	•
Glutamate	• NMDA receptor antagonist • mGluR5 antagonists • Positive allosteric modulator of mGluR4 • Glutamate release inhibitor	• Non-selective: amantadine and amantadine extended-release formulation, dextromethorphan, memantine, safinamide (glutamate release inhibitor) • Selective to mGluR5: mavoglurant (AFQ056) and dipraglurant (ADX48621) • Selective to mGluR4: foliglurax (PXT002331)	• Improve dyskinesias • Improve duration of action of levodopa (e.g. safinamide)	• Amantadine extended-release formulations: GOCOVRI approved after results showed dose-dependent decrease in dyskinesia (2017); OSMOLEX extended-release formulation approved for parkinsonism (2018) • Safinamide (XADAGO) approved in 2017 as adjunctive to levodopa to increase ‘on’ time • Mavoglurant (AFQ056): ceased (failed in phase II trial and nonmotor adverse effects were reported) • Dextromethorphan/ quinidine helps minimally with LID (NCT01767129) • Dipraglurant (ADX48621) appears to be safe and well tolerated in phase IIa	•

Neurotransmitter	Target and/or receptor	Medications	Effect on motor symptoms	Clinical trials updates	Future challeng
				trial[226], with some evidence that it reduces peak-dose dyskinesia	
Noradrenaline	• Locus coeruleus brainstem noradrenergic circuits might affect gait and balance • Improvement of attention might have an indirect effect on preventing falls	• Methylphenidate • Atomoxetine	Possible effect on FOG although evidence not strong	• Methylphenidate and atomoxetine to enhance gait and balance in PD (NCT02879136) • TAME-PD	Larger c needed v analysis

5-HT, 5-hydroxytryptamine (serotonin); FOG, freezing of gait; LID, levodopa-induced dyskinesia; mGluR, metabotropic glutamate receptor; MPTP, 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine; NMDA, *N*-methyl-d-aspartate; PD, Parkinson disease.

Table 5 |

Enzymatic or neurotrophic factor therapies for PD using direct infusion or gene therapy

Therapy and trial(s)	Trial design	Outcome	Challenges and future directions
Symptomatic therapies			
Human AADC gene therapy for PD: three trials[145,147,227]	Phase I open-label studies, *n* = 21 patients total	Favourable with evidence of radiological response and clinical improvement. Four-year clinical follow-up showed modest increase in UPDRS scores[228]	Small sample and absence of controls. Unclear what is the best vector dose and delivery method. Will benefit from a randomized trial and longer follow-up
Safety study of AADC gene therapy (VY-AADC01) (NCT01973543)	Phase I open-label study, aiming to recruit 15 participants	Initial report of the ongoing study confirmed safety and tolerability of VY-AADC01	Study is employing a high vector concentration and a different surgical technique using MRI guidance for precision in vector delivery. Estimated completion in December 2019
ProSavin, a lentiviral vector-based gene therapy (encoding AADC, TH and GCH1)[229]	Phase I/II open-label trial (*n* = 15)	Favourable with significant improvement of motor UPDRS III score (mean score decreased by 11 points) and medication reduction at 12-month follow-up	Small sample, increased on-medication dyskinesias and motor fluctuations. A second-generation gene therapy trial, OXB-102, is in progress
AAV-mediated expression of *GAD* for PD: two trials[146,230]	One phase I trial (*n* = 12) and one phase II trial (*n* = 37)	Favourable radiological and clinical outcomes with reduction in UPDRS motor scores at 6 months (23.1%) compared with sham surgery (12.7%). Benefit persisted at 12 months[152]	Safe and effective in phase II. No phase III trials planned yet
Disease-modifying therapies			
GDNF infusion: two open-label pilot studies[231,232] and two randomized double-blinded studies[233]	• Phase I open-label study (*n* = 5), bilateral putamenal delivery • Phase I open-label study (*n* = 10), unilateral putamenal delivery • Phase I/II randomized double-blinded study (*n* = 34 with 1:1 randomization), bilateral putamenal delivery • Phase I/II randomized double-blinded study (*n* = 41) followed by a 9-month open-label extension study	• Open-label trials found favourable radiological (increased putamenal[18] F-l-DOPA uptake) and clinical outcomes (39% decrease in UPDRS motor scores with bilateral putamenal delivery versus 30% decrease with unilateral putamenal delivery) • Persistent clinical benefit without serious adverse events in a 2-year follow-up study[234] • RCT found favourable radiological benefit that did not translate into clinical benefit	• Animal models revealed cerebellar injury with putamen liatermin infusion • Three patients developed antiliatermin antibodies, which can cross-react with endogenous GDNF • Novel method of administration of GDNF by the Bristol study group through convection-enhanced delivery rather than diffusion- dependent delivery. Despite the study not meeting the primary end point, the open-label extension study is still ongoing[235]
NRTN (vector delivery): four trials in total. AAV2-NRTN CERE-120 in bilateral putamen[162,163] and dual targets (putamen and SN)[236,237]	• In bilateral putamen: one open-label (*n* = 12) and one randomized study (*n* = 58 total, 38 patients were randomly assigned in treatment arm) • Dual target putamen and SN: open-label phase I (*n* = 6 patients).	• In bilateral putamen: UPDRS motor scores improved at 12 months (reduction of 14 points) in phase I trial. No statistically significant difference was found in motor UPDRS scores at 12	• Putamen: in RCT, 5 patients developed tumours (*n* = 3 patients in treatment arm and *n* = 2 patients in sham-surgery arm) • Failure to reveal clinical benefit in dual targeting (putamen and SNc) raised doubts

Therapy and trial(s)	Trial design	Outcome	Challenges and future directions
	RCT (n = 51 total, 24 patients were randomly assigned to the treatment arm)	months when both arms were compared in the randomized study • Dual target putamen and SN: safe and feasible in phase I. In the RCT, no statistically significant difference was found when UPDRS motor scores were compared in the two arms	about trophic factors, especially NRTN, and methods of factor delivery in the nigrostriatal system
GDNF (vector delivery): AAV2-GDNF for advanced PD (NCT01621581)	Phase I open-label study with aim to recruit 25 patients	NA	Estimated completion date January 2027. Status active but not recruiting now
CDNF infusion: safety of CDNF by brain infusion in patients with PD (NCT03295786)	Phase I/II randomized double-blinded study aiming to enrol 18 participants	NA	Estimated completion date in 2019

AADC, aromatic-l-amino acid decarboxylase; AAV, adeno-associated virus; CDNF, cerebral dopamine neurotrophic factor; GCH1, GTP cyclohydrolase 1; GDNF, glial cell-derived neurotrophic factor; l-DOPA, 3,4-dihydroxyphenylalanine; NA, not applicable; NRTN, neurturin; PD, Parkinson disease; RCT, randomized controlled trial; SN, substantia nigra; SNc, substantia nigra pars compacta; TH, tyrosine 3-monooxygenase; UPDRS, Unified Parkinson's DiseaseRating Scale.