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Prospects for Disease Slowing in Parkinson Disease

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Abstract

The increasing prevalence of Parkinson disease (PD) highlights the need to develop interventions aimed at slowing or halting its progression. As a result of sophisticated disease modeling in preclinical studies, and refinement of specific clinical/genetic/pathological profiles, our understanding of PD pathogenesis has grown over the years, leading to the identification of several targets for disease modification. This has translated to the development of targeted therapies, many of which have entered clinical trials. Nonetheless, up until now, none of these treatments have satisfactorily shown disease-modifying effects in PD. In this review, we present the most up-to-date disease-modifying pharmacological interventions in the clinical trial pipeline for PD. We focus on agents that have reached more advanced stages of clinical trials testing, highlighting both positive and negative results, and critically reflect on strengths, weaknesses, and challenges of current disease-modifying therapeutic avenues in PD.

If you think research is expensive, try disease.

—Mary Lasker

1. INTRODUCTION

Neurological disorders are the most common cause of human disability. Among these, some data suggest Parkinson disease (PD) shows the fastest growth rate (1), with the number of people with PD estimated to nearly double by 2040 (2). This will affect economies and societies with a 50% rise in direct medical and nonmedical costs, loss of social productivity from both people with PD and their caregivers, paid care expenditures, and nursing home costs (2, 3).

The onset of PD is approximately 60 years of age and is characterized by the gradual onset of bradykinesia, accompanied by the presence of either rest tremor, rigidity, or postural instability. The two main pathological hallmarks of PD are the selective loss of dopaminergic neurons from the substantia nigra pars compacta and the accumulation of aggregated α-synuclein in the brainstem and cortical regions (4), with more than 50% of the nigral dopaminergic neurons lost at the time of clinical diagnosis (5).

Current treatments available for PD do not arrest disease progression. Since 2020, an annual report on the PD drug development pipeline has been generated (6). As highlighted in the last report published in 2023 (7), currently tested disease-modifying treatments address a wide range of mechanisms and pathways relevant to PD pathogenesis.

In this review, we summarize the most recent evidence regarding disease-modifying treatments in PD, focusing on those compounds that have entered Phase II–III randomized controlled trials (RCTs) and those with available results (summarized in **Figure 1**). We group treatments by pathogenic mechanism/target. Each section presents a brief introduction explaining the rationale behind the mechanism/target, an overview of the selected studies testing disease-modifying treatments, and, if relevant, a brief discussion about the pitfalls associated with the treatments presented. Then, we highlight the ongoing challenges in disease-modifying trials.

2. TREATMENTS TARGETING α-SYNUCLEIN

α-Synuclein is a small, natively unfolded protein of 140 amino acids (8) that is highly expressed in the central nervous system (CNS), where it composes 1% of all cytosolic proteins (9). Physiologically, the main role of α-synuclein is vesicular transport and neurotransmitter release control through effects on the SNARE complex (10). Pathologically, α-synuclein can misfold and aggregate into fibrillar assemblies that mainly constitute Lewy neurites and Lewy bodies (11), also formed by a multitude of fragmented membranes, organelles (e.g., lysosomes and mitochondria), and lipids (12). Common traits that make neurons more vulnerable to α-synuclein aggregation include a long and highly branched axon, elevated calcium entry, reactive oxygen species and reactive nitrogen species, and decreased autophagic clearance resulting from mitochondrial damage (5). In addition to abnormal aggregation, misfolded α-synuclein forms can spread from cell to cell and seed aggregation of native α-synuclein in a prion-like fashion (13). This, together with the evidence that genetic variants, duplications, and triplications of the *SNCA* gene are linked to rare, autosomal dominant forms of PD (14–16), has made toxic forms of aggregated α-synuclein the most attractive targets for disease-modifying treatments in PD, with current strategies mainly aiming to either increase α-synuclein protein clearance or prevent α-synuclein accumulation (17).

2.1. Passive Immunization

The first strategy against α-synuclein (i.e., the use of antibodies targeting different conformational forms of α-synuclein) showed promising results in preclinical studies. These positive results

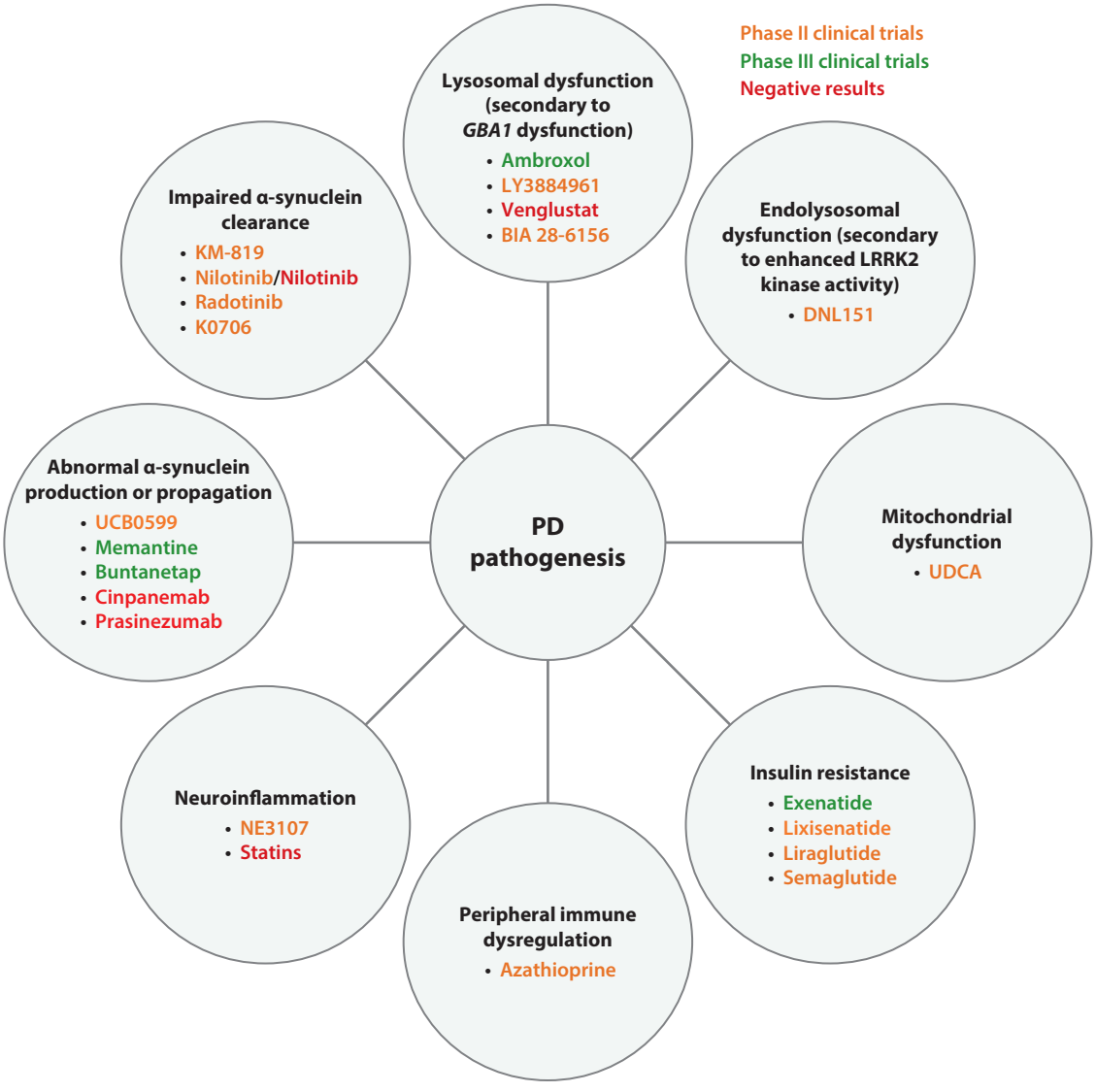

Figure 1

Overview of pathogenic mechanisms and corresponding targeted disease-modifying treatments in Parkinson disease. For each mechanism/target, the interventions that have entered Phase II or III clinical trials are in orange and green, respectively. Interventions with published negative results in advanced phases of clinical trials are in red. Abbreviation: PD, Parkinson disease; UDCA, ursodeoxycholic acid.

were not confirmed in Phase II clinical trials, where two human-derived monoclonal antibodies, cinpanemab and prasinezumab, both failed (18, 19).

Cinpanemab (also known as BIIB054) preferentially binds to aggregated forms of extracellular α-synuclein. In a Phase I trial, concentrations of cinpanemab were increased in both serum and cerebrospinal fluid (CSF) of healthy volunteers and people with PD, in a dose-dependent manner, with evidence of cinpanemab/α-synuclein complex formation in plasma, suggesting biological activity (20). In the subsequent 52-week, Phase II, multicenter RCT (SPARK; NCT03318523),

intravenous administration of cinpanemab every 4 weeks at three different doses (250 mg, 1,250 mg, or 3,500 mg) was compared to placebo (18). Participants who initially received placebo were started on cinpanemab at week 52 (delayed-start group) and were evaluated against the early-start group at 72 weeks. The effect of cinpanemab on the progression of motor and nonmotor symptoms, activities of daily living, and dopamine transporter–single photon emission computed tomography (DaT-SPECT) imaging biomarkers at 52 weeks did not differ from placebo. There was also no difference in the delayed-start analysis at 72 weeks, or in the start of symptomatic treatment for PD, suggesting absence of disease-modifying effect (18).

Similar results were obtained with prasinezumab (also known as PRX002), another monoclonal antibody that selectively binds aggregated α-synuclein at the C-terminal of the protein (19). Positive results of target engagement (dose-dependent reduction in α-synuclein levels in free serum after treatment) and brain penetration were observed in Phase I trials conducted on healthy volunteers and people with PD (21, 22). The PASADENA trial (NCT03100149) was a Phase II RCT testing efficacy and safety of two doses (1,500 mg and 4,500 mg) of prasinezumab in people with early-stage PD. No differences in motor and nonmotor symptoms, or DaT-SPECT imaging markers, were observed between the prasinezumab and placebo arms, with high incidence of serious adverse events (~7%) and infusion reactions (up to 34%) in the prasinezumab group (19). An ongoing, 5-year open-label extension is under way. Another Phase IIb RCT evaluating intravenous prasinezumab in people with early-stage PD (PADOVA; NCT04777331) is also planned (although not actively recruiting).

Another anti-α-synuclein monoclonal antibody, UCB7853, has been tested in a recently completed Phase I study (NCT04651153).

2.2. Active Immunization

The second approach used to target α-synuclein is active immunization. This pathway acts through the immune presentation of a small fragment of α-synuclein to trigger an antigen-specific immune response (23). Relative to passive immunization, vaccination requires less frequent administration and is associated with reduced production costs (23). Three compounds within this category have currently reached Phase I clinical trial.

The safety, tolerability, and immunogenicity of UB-312, a synthetic peptide-based vaccine, are under evaluation in a Phase Ib study (NCT05634876) in people with PD and multiple system atrophy (MSA), another neurodegenerative disorder characterized by accumulation of abnormal α-synuclein. Study completion is expected in 2025. Two other short peptide formulations targeted against α-synuclein, PD01A and PD03A, showed good safety and tolerability and satisfactory immune response (24, 25), but Phase II studies are needed to further assess the safety and efficacy of these drugs.

2.3. Inhibition of α-Synuclein Aggregation and Extracellular α-Synuclein Propagation

The third approach to target α-synuclein consists of inhibiting α-synuclein aggregation or extracellular α-synuclein propagation.

The orally administered small-molecule inhibitor of α-synuclein misfolding, UCB0599, which displayed an acceptable safety, tolerability, and pharmacokinetics profile in a Phase I/Ib study (26), is currently under evaluation in a Phase IIa RCT in people with early-stage PD (NCT04658186), with results expected in 2024. The same molecule is also under evaluation in a long-term study investigating the pharmacodynamic effects of UCB0599 on brain pathophysiology in early-start versus delayed-start participants.

The novel oligomer modulator anle138b [3-(1,3-benzodioxol-5-yl)-5-(3-bromophenyl)-1*H*-pyrazole] is an aggregation inhibitor that modulates toxic oligomers (27), and it showed good results in different in vivo models of α-synucleinopathies (28, 29). Following positive results of a Phase I study conducted on healthy subjects (30), a second Phase I RCT multiple ascending dose study in people with mild to moderate PD has recently completed recruitment (NCT04685265).

Preclinical studies showed that memantine, an antagonist of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor, may inhibit cell-to-cell transmission of extracellular α-synuclein in in vitro and in vivo models by blocking the clathrin-mediated endocytosis of extracellular α-synuclein fibrils via modulation of the interaction between α-synuclein and NMDA receptors (31). Results from a Phase III clinical trial (NCT03858270) evaluating the effects of memantine in people with PD should be released in 2024.

2.4. Enhanced α-Synuclein Clearance

The autophagy machinery is one of the mechanisms that regulate intracellular homeostasis of α-synuclein (32). Fas-associated factor 1 (FAF1) is a negative regulator of α-synuclein clearance; therefore, FAF1-targeting compounds could reduce α-synuclein accumulation (33). Among those, the compound KM-819 was well tolerated by healthy volunteers in a Phase I study (34) and reduced accumulation of monomeric and toxic forms of α-synuclein in preclinical models (33, 35). KM-819 is now under investigation in a Phase II study (NCT05670782) conducted on healthy older adults and people with PD.

c-Abl is a member of the family of tyrosine kinases that is activated by cellular stressors and regulates several crucial cellular processes, including cell survival and growth factor signaling (36, 37). Inhibition of c-Abl can increase the autophagic flux in neuronal cells, decrease accumulation of pathological α-synuclein, and delay disease onset in transgenic mice overexpressing the human mutant A53T α-synuclein (38). For these reasons, c-Abl kinase inhibitors [e.g., nilotinib, radotinib, risvodetinib (IkT-148009), vodobatinib (K0706)] have entered clinical studies.

The most studied compound so far is nilotinib. Nilotinib showed good preclinical evidence in animal models of PD, with improved motor function, reduced misfolded α-synuclein, and rescued dopaminergic neuronal loss (39, 40). After demonstrating good CNS penetrance and beneficial effects in reducing α-synuclein levels in plasma and increasing dopamine metabolites in a small pilot study of people with PD and dementia with Lewy bodies (41), nilotinib entered three Phase II clinical trials. Encouraging results came from a single-center RCT that enrolled 75 people with PD randomized to receive orally administered nilotinib (150 mg or 300 mg) versus placebo for 12 months (NCT02954978) (42). The treated arm showed increased levels of dopamine metabolites and reduction of α-synuclein oligomers in CSF, with a good safety and tolerability profile (42). In an open-label extension of this trial, at 15 months participants were randomly reassigned to nilotinib 150 mg versus 300 mg for a further 12 months (43). The study met its primary end points (long-term safety and tolerability of nilotinib treatment). Moreover, exploratory clinical outcomes (stable cognitive and motor abilities, as well as activities of daily living, over 27 months) supported the evaluation of nilotinib 300 mg in a multicenter, Phase III trial (43). Unfortunately, contrary results were obtained from a 6-month, multicenter RCT of 76 people with moderately advanced PD assigned to receive either nilotinib 150 mg or 300 mg daily or placebo for 6 months (44). Both doses had acceptable safety and tolerability profiles; however, they showed worsening of motor function over time. Nilotinib concentration was less than 0.3% in CSF compared to serum, and no changes in dopamine metabolites levels were observed in treated arms (44).

The effects of radotinib and K0706 in people with PD will be evaluated in Phase II RCTs (NCT04691661, NCT03655236). A Phase I study will assess single and multiple doses of IkT-148009 in healthy elderly adults and people with PD (NCT04350177).

2.5. Decreased α-Synuclein Production

The limitation of the approaches presented above is that they cannot target intracellular Lewy body inclusions (45). On the contrary, strategies that inhibit α-synuclein production by targeting intracellular *SNCA* RNA can suppress protein levels and reach the intracellular compartment (46).

Within this group, promising therapeutic strategies are antisense oligonucleotides (ASOs). In rodent preformed fibril models of PD, α-synuclein ASOs reduced α-synuclein production and prevented dopaminergic cell dysfunction (45). These results might support the use of α-synuclein ASOs as potential disease-modifying treatments for PD (45), but none of these treatments have yet entered clinical trial.

By targeting an iron-response element in the 5′ untranslated region of *SNCA* mRNA, the orally bioavailable small-molecule buntanetap could suppress *SNCA* translation and normalize the protein levels in animal models (47). In a Phase II RCT, buntanetap was safe and well tolerated, improved motor function, and ameliorated inflammatory and neurodegenerative markers in people with PD (48). These encouraging results prompted testing of the drug in a Phase III study that has just completed recruitment (NCT05357989).

2.6. Caveats and Pitfalls

The negative results of Phase II trials on passive immunization, together with the discrepancies in the studies testing c-Abl inhibitors, raise questions about the role of α-synuclein as a target for disease modification in PD. To date, two-thirds of the PD clinical development pipeline for disease modification targets α-synuclein aggregation, indicating that the pipeline has been focused mostly on the expected toxicity of α-synuclein in its aggregated form (17). However, there is no strong support for a primary pathogenic role of α-synuclein and Lewy bodies in PD other than in the α-synuclein genetic forms. The severity of nigral neuron loss was not associated with the distribution or density of Lewy bodies, and the burden of Lewy bodies pathology was not associated with disease duration or symptoms in large postmortem studies (49, 50). Moreover, α-synuclein and Lewy body pathology can be absent in PD cases (e.g., most individuals carrying variants in the *PRKN* gene) (51), and levels of soluble α-synuclein were slightly reduced in a cohort of people with early-stage PD relative to controls (52). Since α-synuclein is fundamental to maintaining cell homeostasis (9), the hypothesis that loss of functional α-synuclein might play a role in PD pathogenesis has been formulated (17). Some researchers suggest a shift from the current paradigm of proteinopathy (toxic gain of function) to the novel paradigm of proteinopenia (toxic loss of function) in PD (53). This novel paradigm is based, for instance, on the evidence that knockdown of endogenous α-synuclein in aged nonhuman primates or rats can lead to nigrostriatal degeneration and behavioral changes (54, 55).

Treatments aiming to restore physiological levels of α-synuclein could represent a new therapeutic avenue in PD. At which stage of the disease course the preservation of functional levels of α-synuclein can help prevent progression remains uncertain. Furthermore, if the proteinopenia hypothesis is correct, those strategies to reduce α-synuclein levels may prove counterproductive.

3. GENE THERAPY: *GBA1* AND *LRRK2*

Although most people with PD do not have a currently identifiable genetic cause, variants in the glucosylceramidase beta 1 (*GBA1*) and leucine-rich repeat kinase 2 (*LRRK2*) genes are relatively

common in cases of sporadic PD (found in 10–15% and 1–2% of PD cases, respectively, as opposed to less than 1% of healthy individuals) (56, 57). These variants can be considered either genetic risk factors or autosomal dominant pathogenic variants with incomplete penetrance (58). In recent years, substantial effort has been committed to understanding the implications of these genetic variants for PD pathogenesis and the consequent development of targeted treatments.

3.1. *GBA1*

The *GBA1* gene encodes glucocerebrosidase (GCase, or acid-β-glucosidase), a 60-kDa lysosomal hydrolase enzyme that hydrolyzes glucosylceramide (GL-1) to ceramide and glucose. Biallelic pathogenic variants in *GBA1* cause Gaucher disease, an autosomal recessive lysosomal storage disorder characterized by the accumulation of GL-1 in the lysosome of macrophages (59, 60). The deacylated form of GL-1, glucosylsphingosine (lyso-GL-1), also accumulates in Gaucher disease (61).

Heterozygous carriers of *GBA1* variants have increased risk of PD, with odds ratio varying from 1.5 to 30 (62). *GBA1*-PD is a clinical syndrome that resembles idiopathic PD, with the exception of carriers of severe pathogenic variants who tend to present with younger age at onset, more severe nonmotor symptoms, and more rapid progression (63).

Physiologically, GCase protein is synthesized, folded in the endoplasmic reticulum (ER), translocated along the secretory pathway from the ER to the Golgi apparatus, and then trafficked to endosomes and lysosomes, where it is activated (63). Several mechanisms have been linked to GCase dysfunction in the presence of *GBA1* variants, from loss of transcription/translation to increased ER stress to unfolded protein response activated by misfolded GCase protein in the ER (64, 65). Accumulation of GCase substrates, GL-1 and lyso-GL-1, could be expected in *GBA1*-PD. Levels of GL-1 and lyso-GL-1 were increased in plasma and CSF of individuals with *GBA1*-PD compared with people with PD without *GBA1* variants (66–68); however, there was no evidence of sphingolipid accumulation in postmortem brains of individuals with *GBA1*-PD (69). GL-1 and lyso-GL-1 accumulated in the substantia nigra pars compacta of idiopathic PD brains compared with matched controls (70, 71). The role of sphingolipids in *GBA1*-PD and PD pathogenesis thus remains controversial.

Considering the proposed gain-of-function and loss-of-function mechanisms in association with *GBA1*-PD pathogenesis (72), three main *GBA1*-targeted strategies have been investigated in the disease-modifying therapies development pipeline for PD.

3.1.1. Promotion of post-ER trafficking of mutant GCase. The most successful and promising *GBA1*-targeted approach is the use of small-molecule, brain-penetrant chaperones able to stabilize and refold GCase misfolded proteins, hence promoting trafficking of mutant GCase from the ER to the Golgi apparatus and lysosomes (64, 73).

Among the three existing groups of GCase molecular chaperones (i.e., inhibitory, noninhibitory, and mixed-type), the mixed-type chaperone ambroxol has entered Phase III clinical trial. Ambroxol acts in a pH-dependent manner, with an inhibitory activity that is maximal in the cytoplasmic neutral pH, intermediate in the ER, and undetectable in the lysosomal acidic pH (74). Extensive in vitro and in vivo evidence supports the beneficial effects of ambroxol in restoring GCase activity, reducing levels of toxic forms of α-synuclein, and rescuing mitochondrial and lysosomal function (75–77). A Phase II, single-center, open-label study (Aim-PD; NCT02941822) evaluated ambroxol (1,260 mg/day) over 6 months in a cohort of 17 people with PD, 8 of whom carried a *GBA1* variant (78). Ambroxol showed good target engagement, with increased levels of GCase protein in CSF. Furthermore, increased total concentration of α-synuclein in CSF and improved motor function were observed in participants at 6 months

(78). Given these promising results, a Phase III, multicenter RCT (ASPro-PD; NCT05778617) will enroll 330 people with PD, with and without *GBA1* variants, randomized to receive either ambroxol or placebo. Changes in motor and nonmotor function will be evaluated at 104 weeks compared to baseline. Recruitment is expected to start in 2024. In the meantime, results from two other Phase II RCTs testing ambroxol in *GBA1*-associated PD will likely become available. In one study (AMBITIOUS; NCT05287503), 60 individuals with *GBA1*-PD will be randomly assigned to receive ambroxol (1,200 mg/day) or placebo over 52 weeks; study completion is expected in 2024. In the other study (NCT02914366), 75 individuals with mild to moderate PD-dementia will be randomized to receive high- or low-dose ambroxol (1,050 or 525 mg/day) or placebo (79). Both studies will evaluate changes in cognitive function as primary end points.

The group of noninhibitory chaperones is formed of compounds that can restore posttranslational folding of mutant proteins by binding GCase outside the active site, thus preventing enzymatic inhibition (80). Among these compounds, the allosteric GCase activator BIA 28-6156 (also known as LTI-291) showed a positive safety, pharmacokinetics, and pharmacodynamics profile in healthy volunteers. No clear target engagement was observed, but this could have been explained by the fact that healthy volunteers are expected to show normal GCase function (81). BIA 28-6156 is currently under evaluation in a Phase II RCT (ACTIVATE; NCT05819359) that aims to enroll 237 individuals with *GBA1*-PD. Participants will be randomized in a 1:1:1 ratio (two doses of BIA 28-6156, 10 or 60 mg/day, and placebo) and receive treatment for 78 weeks followed by a 4-week safety follow-up period.

3.1.2. Restoration of enzyme levels. Another *GBA1*-targeted approach is gene therapy, with the goal to restore adequate levels of GCase protein and enzymatic activity. Encouraging results came from several in vivo models, where gene therapy was able to not only increase GCase activity but also decrease α-synuclein levels and improve behavioral features (82, 83). An open-label, Phase I/II, multicenter clinical trial testing intracisternal administration of high-dose and low-dose LY3884961 (formerly PR001) in PD has started (PRV-PD101, PROPEL; NCT04127578). Participants are people with moderate to severe PD carrying at least one pathogenic *GBA1* variant. Primary outcomes are safety, tolerability, immunogenicity, biomarkers profile, and clinical effects.

3.1.3. Substrate reduction therapy. The last approach in *GBA1*-targeted therapy is reduction of substrate accumulation by direct inhibition of the GL-1 synthase enzyme, although the pathogenic role of sphingolipids in *GBA1*-PD onset is uncertain.

Venglustat (GZ/SAR402671) is a brain-penetrant, GL-1 synthase inhibitor that reduced accumulation of substrates and proteins such as α-synuclein and prevented development of memory deficits in mouse models of Gaucher disease–related synucleinopathy (84). Venglustat was tested in a Phase II, multicenter RCT conducted on individuals with *GBA1*-PD (MOVES-PD; NCT02906020). Venglustat showed a good safety and tolerability profile, target engagement, and CNS penetration (85). The maximum dose tolerated (15 mg/day) was then tested in a 52-week RCT and followed by a 104-week open-label extension period (86). Despite good target engagement (75% reduction in GL-1 levels in CSF and plasma from baseline to week 52), not only did venglustat not meet its primary end point (i.e., improvement in motor and nonmotor function) but the venglustat group showed a trend toward greater deterioration in motor and nonmotor scores from baseline, suggesting a negative symptomatic effect. The results of the study also raise further questions about the role of substrate accumulation in clinical progression of *GBA1*-PD (86).

Another brain-penetrant GL-1 synthase inhibitor, GZ667161, was tested in animal models (i.e., α-synuclein-overexpressing mice and mice carrying homozygous *GBA1* variants) and improved

behavioral features and reduced GL-1, lyso-GL-1, and α-synuclein accumulation (87); however, this molecule has not yet been tested in humans.

3.2. *LRRK2*

The LRRK2 protein is a large, multidomain protein kinase that is composed of two catalytic domains [i.e., the Ras-of-complex (ROC) GTPase domain in tandem with the C-terminal of ROC (COR) domain, and the adjacent kinase domain], an ankyrin repeat domain, an LRR domain, and a WD40 domain (88). More than 100 *LRRK2* variants have been described; among those, the G2019S and I2020T (located in the kinase domain), the R1441C, R1441G, R1441H, and N1437H (located in the ROC domain), and the Y1699C (located in the COR domain) variants have been shown to be pathogenic (89). The G2019S variant is the most common in people with PD, found in approximately 1% of sporadic PD cases and up to 4% of familial PD cases worldwide (56). In Ashkenazi Jewish and North African communities, these percentages increase to 29% and 37% of familial PD cases, respectively (90, 91).

Clinically, *LRRK2*-PD cases present a relatively benign phenotype, characterized by mild motor symptoms, good response to dopaminergic treatment, and less frequent nonmotor symptoms (92–94).

Physiologically, LRRK2 kinase controls several intracellular processes, including vesicle trafficking, autophagy, and the endolysosomal pathway (95). The converging effect of pathogenic *LRRK2* variants is an enhancement in kinase activity associated with autophosphorylation and phosphorylation of certain Rab small GTPases (88, 96), resulting in accumulation of autophagosomes and reduction of lysosomes (97), alteration in protein aggregate clearance (89), and neuronal toxicity (98).

There is a wide range of therapeutic strategies to reduce LRRK2 protein function in PD, which include kinase inhibition, LRRK2 GTPase activity inhibition, and *LRRK2* mRNA knockdown (99).

3.2.1. ATP-competitive kinase inhibition. The greatest success in LRRK2-targeted therapy development has been reached by type I, ATP-competitive LRRK2 kinase inhibitors. Since the first inhibitors (e.g., staurosporine) were tested (100), impressive progress has been achieved in the field, with several candidate drugs now under evaluation in Phase I–II clinical trials.

Type I kinase inhibitors compete with ATP to bind the ATP-binding pocket within the kinase domain (99). To allow this interaction, the kinase domain activation loop needs to be in the active conformation (99). A 180° rotation of the conserved Asp-Phe-Gly (DFG) motif in the kinase domain activation loop transforms the active form of LRRK2 (DFG-in) into the inactive form (DFG-out) (101), the latter constituting the binding site of type II inhibitors (see Section 3.2.2). Considering the effect of *LRRK2* variants, the most common variant, G2019S, for instance, results in the stabilization of the active conformation of LRRK2 kinase, thereby increasing LRRK2 kinase activity (102). Among type I inhibitors, two compounds (BIIB122/DNL151 and DNL201) have entered clinical studies.

BIIB122/DNL151 was tested in a Phase I and Ib study (NCT04056689) to assess safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy volunteers and people with mild to moderate PD, with positive outcomes (103). Therefore, BIIB122/DNL151 is now under investigation in a Phase IIb, multicenter RCT (LUMA; NCT05348785) to assess safety and impact on disease progression in people with early-stage PD with and without *LRRK2* variants. A total of 640 participants will be recruited and receive treatment for a minimum of 48 weeks and a maximum of 144 weeks. Primary outcome will be time to motor worsening over the treatment period. Study completion is expected in 2025. A Phase III study (LIGHTHOUSE;

NCT05418673) investigating BIIB122/DNL151 in *LRRK2*-PD commenced in September 2022. Biogen and Denali announced early discontinuation of the LIGHTHOUSE trial in 2023 to focus their efforts on the LUMA study (104).

The second ATP-competitive, LRRK2 kinase inhibitor tested as a potentially disease-modifying treatment in PD is DNL201 (previously known as GNE-0877). Based on the evidence of improved lysosomal function in vitro, this CNS-penetrant, selective, small-molecule compound entered a Phase I and Ib study in healthy volunteers and people with PD, showing good tolerability, CNS penetration, target engagement, and alteration of downstream lysosomal biomarkers (105). Denali and Biogen decided to advance BIIB122/DNL151 and keep DNL201 only as a backup, so no further developments of DNL201 have been announced.

Other type I inhibitors, WXWH0226 and NEU-723 (NCT05633745), have also recently entered Phase I clinical trials (101), with results to be released possibly in 2024.

3.2.2. ATP-noncompetitive LRRK2 kinase inhibition. Type II kinase inhibitors bind kinase domain activation loops in the inactive conformation (DGF-out) and thus reduce kinase activity by gating access to ATP rather than competing with ATP (99). These compounds reduced the formation of LRRK2 filaments in cells and blocked microtubule-based motility (106). However, because the two pathogenic variants G2019S and I2020T stabilize the LRRK2 kinase domain activation loop in the active conformation (DFG-in), type II kinase inhibitors are less effective in patients carrying these variants (99).

An alternative approach to reduce kinase activity in an ATP-noncompetitive fashion is to use allosteric kinase inhibitors that bind the kinase outside the ATP-binding site (99). Through a high-throughput screen, the physiological form of vitamin B12, 5′-deoxyadenosylcobalamin (AdoCbl), has been recently recognized as a mixed-type allosteric inhibitor of LRRK2 kinase activity (107). Preclinical in vitro and in vivo evidence supports the beneficial effect on neuronal death and dopamine release exerted by AdoCbl (107). This compound should deserve further evaluation as a novel LRRK2-targeted therapy in PD.

3.2.3. LRRK2 GTPase activity inhibition. Although the kinase domain remains the most explored target, inhibition of the enzymatic GTPase domain could also represent an interesting approach to target LRRK2. So far, three GTP-binding inhibitors (compounds 68 and 70, and FX2149) have been successfully applied in preclinical studies, with positive outcomes on neuronal degeneration and microglia activation (108–110). None of these compounds have yet been tested in humans.

3.2.4. Knockdown of *LRRK2* mRNA. Preclinical evidence suggested that intracerebral injection of LRRK2 ASOs was able to reduce LRRK2 protein levels and fibril-induced α-synuclein inclusions in mice (111). Moreover, animals exposed to α-synuclein fibrils treated with LRRK2 ASOs preserved dopamine neurons compared to control mice (111). Intrathecal injection of BIIB094, an LRRK2 ASO, is currently under evaluation in a Phase I study (REASON; NCT03976349). The study is enrolling people with PD with and without *LRRK2* variants, and study completion is expected in 2024.

3.3. Caveats and Pitfalls

Despite the remarkable progress in *GBA1*- and *LRRK2*-targeted drug development in PD, several questions remain unanswered.

First, are people with PD without *GBA1* or *LRRK2* variants good candidates for these treatments? It is well known that GCase activity is reduced in idiopathic PD brain compared to controls and tends to decrease naturally with age (71, 112). Moreover, preliminary results from open-label

studies showed that GCase-targeted therapies might be equally effective in individuals with *GBA1*-PD and idiopathic PD (78). Similarly, increased LRRK2 activity was detected in postmortem brains (113) and peripheral blood mononuclear cells (105) from people with idiopathic PD. Centrosomal alterations in peripheral cells were detected in *LRRK2*-PD cases as well as in a subset of early-stage idiopathic PD, and these were mitigated by LRRK2 kinase inhibition (114).

Second, which biomarkers can reliably measure GCase or LRRK2 modulation in clinical trials? Several putative candidate biomarkers have been explored over the years, yet none of them convincingly showed an association with disease progression or severity (115, 116). Bis(monoacylglycerol)phosphate (BMP) is a biomarker of lysosomal dysregulation. Decreased levels of BMP in urine were found in Lrrk2 knockout mice and in nonhuman primates treated with LRRK2 kinase inhibitors (117). Several case control studies conducted on people with PD carrying either *LRRK2* G2019S or R1441G/C variants also showed elevated levels of BMP in urine (118–120); however, a longitudinal study failed to identify any correlation with clinical progression, suggesting that BMP could be used to reflect target modulation but not as a disease progression biomarker in clinical trials (120).

The third and probably most important question is, Are these treatments safe? Many concerns have been raised around the safety of LRRK2 inhibitors considering the lung toxicity reported for nonhuman primates treated with these molecules (117). Subsequent studies showed that these changes are reversible (121, 122); however, vigilance should remain high.

4. PERIPHERAL IMMUNE DYSFUNCTION AND NEUROINFLAMMATION

Mounting evidence suggests that dysregulation in the peripheral immune system and inflammation play a crucial role in PD pathogenesis. PD is characterized by abnormalities in both innate and adaptive immune systems (123), with a shift toward classical (inflammatory) monocytes (124), and by an impairment in the T lymphocyte compartment, with a reduction in the number and function of regulatory T cells (Tregs) [whose role is to suppress effector T cells (Teffs)] and an increase in the number of Teff subsets with neurotoxic potential (125, 126). Furthermore, several studies report an association between polymorphisms in the human leukocyte antigen region, or enrichment for genes of the adaptive immune system (regulation of leukocyte/lymphocyte activity and cytokine-mediated pathways), and PD susceptibility (127, 128). Therefore, targeting the immune and inflammatory systems has become a strategy to slow down PD progression, and several compounds have reached clinical trials.

Azathioprine, an immunosuppressant drug with well-established efficacy in a wide range of immune-related conditions, is currently under evaluation in a Phase II RCT in PD (AZA-PD; ISRCTN14616801) (123). The study aims to enroll 60 people with early-stage PD with high probability of disease progression. Participants will be treated with azathioprine or placebo for 12 months. The primary end point is change in motor function at 12 months (123). Recruitment for this study has been completed.

Another anti-inflammatory drug applied to PD is 17α-ethynyl-androst-5-ene-3β,7β,17β-triol (NE3107, formerly known as HE3286). NE3107 is an oral small-molecule, blood-brain barrier–permeable, anti-inflammatory insulin sensitizer that binds extracellular signal-regulated kinase (ERK) and selectively inhibits inflammatory mediators (e.g., TNF-α or IFN-γ) driven by the ERK and NF-κB pathways (129). Preclinical evidence supports the involvement of the ERK pathway in PD pathogenesis. Treatment with 6-hydroxydopamine triggered sustained ERK activation contributing to neuronal cell death in vitro, which was prevented by using ERK inhibitors (130). Moreover, postmortem studies showed the presence of granular cytoplasmic aggregates

of phospho-ERK in the substantia nigra of people with PD, more often in those neurons without concomitant α-synuclein pathology, suggesting an early involvement of the ERK pathway in disease pathogenesis (131). A Phase IIa, multicenter RCT evaluated safety, potential drug-drug interactions, and changes in motor function in people with PD receiving 20 mg of NE3107 twice daily versus placebo (NCT05083260). The study was completed in January 2023, but no results have yet been published.

The human recombinant granulocyte-macrophage colony-stimulating factor sargramostim is an immunomodulatory compound that increases Treg numbers or function and reduces or transforms proinflammatory Teff responses, thus protecting dopaminergic neurons (132). An early Phase I trial of sargramostim reported modest improvement in motor function over a 2-month treatment (133). Sargramostim has been subsequently evaluated in a Phase Ib, open-label study (NCT03790670) conducted on a small sample size ($N = 5$ people with PD) where sargramostim was administered for 12 months. The safety and tolerability profile was satisfactory. Sargramostim did not worsen motor function, positively altered immune function, and shifted T cell phenotypes with increased Treg numbers and function (132). Safety and beneficial immune and anti-inflammatory responses after sargramostim were also confirmed over a multiyear (33 months) study (134).

Recent evidence suggests that the NOD-LRR protein family (NLRP3) is activated by α-synuclein aggregates. This in turn exacerbates inflammation in the CNS and activates local microglia and astrocytes to release proinflammatory cytokines and further contribute to α-synuclein aggregation and neuronal loss (135). IZD174 is a small, brain-penetrant NLRP3 inhibitor currently evaluated in a Phase Ib, open-label study in people with PD (NCT04338997).

Other drugs with potential anti-inflammatory properties tested as disease-modifying therapies in PD are statins. Current evidence suggests a potential protective effect of statins on PD development. By inhibiting the mevalonate pathway, statins can exert pleiotropic anti-inflammatory and antioxidant properties in the CNS (136). A recent study that followed French women for 14 years found that the use of lipophilic statins was associated with lower PD incidence, with a dose–response relation for the mean daily dose (136). On a similar note, using routine primary care and UK Biobank data, researchers found that the use of statins was lower in people who developed PD than in those who developed dementia with Lewy bodies and Alzheimer's disease (137). Despite these favorable premises, two clinical trials testing the effect of simvastatin 80 mg/daily (ISRCTN16108482) or lovastatin 80 mg/daily (NCT03242499) as disease-modifying treatments in PD failed their primary outcome (138, 139). Nevertheless, these negative results do not exclude a potential protective effect of statins in healthy individuals on PD development.

5. INSULIN RESISTANCE

Glucagon-like peptide-1 (GLP-1) receptor agonists can cross the blood-brain barrier and stimulate GLP-1 receptors in the brain, with beneficial effects on mitochondrial function, neuroinflammation, protein aggregation, neurotransmitter homeostasis, and behavioral components in animal models of PD (140). GLP-1 receptor agonists are licensed drugs used for type 2 diabetes mellitus. Among those, exenatide provided sustained motor and cognitive improvements in an initial Phase II, open-label study in people with PD (141). A subsequent Phase II RCT confirmed the improved motor outcome after 48 weeks, which persisted after drug withdrawal, although to a lesser extent (142). Whether this effect was truly a disease-modifying effect or simply symptomatic was unclear. To answer this question, a Phase III, multicenter RCT started in 2020 (Exenatide-PD3; NCT04232969). This study will follow people with mild to moderate

PD receiving exenatide (2 mg weekly) or placebo for 96 weeks. Primary outcome is change in motor function in OFF state over the treatment trial period (143). Results are expected in 2024.

In a Phase II RCT conducted on people with early-stage PD, lixisenatide therapy resulted in less progression of motor disability than placebo at 12 months (LIXIPARK; NCT03439943). However, the treatment was associated with gastrointestinal side effects such as nausea and vomiting in 46% and 13% of participants receiving lixisenatide, respectively (144). A RCT tested NLY-01, a brain-penetrant, pegylated, long-lasting version of exenatide, in people with early, untreated PD (145). No improvement in motor and nonmotor features in the treated arm was found. Younger patients preferentially improved compared with older patients, suggesting a possible greater decline in the younger placebo group (145).

Additional Phase II RCTs testing other GLP-1 receptor agonists, such as liraglutide (NCT02953665) and semaglutide (GIPD; NCT03659682), are under way.

6. MISCELLANEOUS

Encouraging results about the potential disease-modifying effect of ursodeoxycholic acid (UDCA) and lithium have been released. Tested in a Phase II RCT in 30 people with PD for 48 weeks, UDCA, which could rescue mitochondrial function in preclinical models of PD, showed a satisfactory safety and tolerability profile, improved ATP hydrolysis in the brain, and improved several gait parameters in the treated group compared to placebo (146). Lithium, which can have multiple neuroprotective effects, including reduced inflammation and oxidative stress and enhanced mitochondrial function, was investigated in a small Phase I, open-label study (NCT04273932) (147). Three different dosages (high, medium, and low) of lithium for 24 weeks were investigated in people with PD. Medium-dose lithium therapy was associated with good engagement of blood-based therapeutic targets and improved magnetic resonance imaging disease progression biomarkers; however, 33% of people with PD on this dose withdrew from the study due to side effects (147). Future studies evaluating lithium tolerability are therefore needed.

7. CONCLUSIONS AND DISCUSSION

In this review, we have summarized the most important disease-modifying therapies already tested and/or under evaluation in clinical trials. We acknowledge that this list is not exhaustive. For instance, we have not discussed stem cell transplant, as most trials testing cell therapies are still at early stages (7). Also, we did not discuss nonpharmacological interventions. However, the efficacy of high-intensity, endurance treadmill exercise is currently being tested in a Phase III study (SPARX3; NCT04284436) (148), and the effect of fecal microbiota transplantation is under evaluation in a Phase I/II RCT (EFFACE-PD; NCT05204641) considering the potential role of physical exercise and gut microbiota in PD progression/pathogenesis (149, 150).

We have highlighted caveats and pitfalls associated with specific targets. Several additional difficulties are encountered in trials for disease-modifying treatments in PD (**Figure 2**). In reality, most novel treatments reach Phase II–III clinical trials and then fail to provide improvements in measured outcomes (151), as reflected by recent failures of inosine (NCT02642393) (152) and deferiprone (NCT02655315) (153) trials. The multi-arm, multi-stage trial design, which enables interim analyses to test target engagement by simultaneously recruiting multiple active treatment arms, could accelerate clinical development of new disease-modifying therapeutics (151). This novel design, combined with the choice of the most appropriate outcome measurements (154, 155), might increase chances of success. Next to trial design, the complex heterogeneity of people with PD may affect clinical trial interpretation (156). In the near future, differentiation of PD

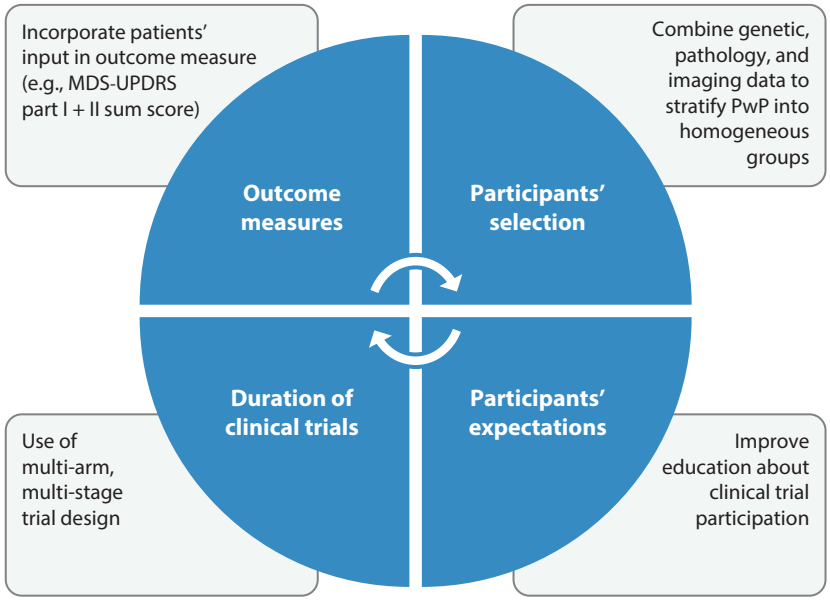

Figure 2

Overview of the main challenges identified in setting up long-term disease-modifying Parkinson disease trials. For each challenge (reported in the *center*), a proposed solution is presented in the outer box. Abbreviations: MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PwP, people with Parkinson disease.

subtypes, based on a combination of genetic, pathology (157), and imaging (158) markers, might overcome this limitation.

Treatments that slow down PD progression are urgently needed to reduce disability, improve quality of life, and relieve burdens on societies and economies. The PD research community is responding to these needs, but it needs to do better.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS

E.M. conceived the manuscript and wrote the first draft. A.H.V.S. conceived and reviewed the manuscript. Both authors read and approved the final version of the manuscript and agreed to be accountable for the work.

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