
Article:
Gonzalez-Robles, C. orcid.org/0000-0001-6809-0127, Bandmann, O. orcid.org/0000-0003-3149-0252 and Schapira, A.H.V. orcid.org/0000-0002-3018-3966 (2025) Neuroprotection in Parkinson disease. Neurology and Therapy, 14 (5). pp. 1747-1767. ISSN: 2193-8253

https://doi.org/10.1007/s40120-025-00793-z

Neurol Ther (2025) 14:1747–1767
https://doi.org/10.1007/s40120-025-00793-z

REVIEW

Neuroprotection in Parkinson Disease

Cristina Gonzalez-Robles · Oliver Bandmann · Anthony H. V. Schapira

Received: April 28, 2025 / Accepted: June 19, 2025 / Published online: July 18, 2025

ABSTRACT

Parkinson disease (PD) is a progressive neurodegenerative condition characterised by tremor, bradykinesia and rigidity, as well as other motor and non-motor symptoms, for which no effective disease-modifying treatments have been discovered. Neuroprotection in PD is limited by its clinical and biological heterogeneity, suboptimal preclinical models, lack of established disease progression biomarkers, complex pathophysiology, the existence of effective symptomatic therapies which hamper the detection of actual disease modification, and trial design. This review discusses the above issues and other important concepts in neuroprotection in PD. The main pathophysiological mechanisms in PD are classified into mitochondrial dysfunction, lysosomal dysfunction, inflammation, protein aggregation/propagation, and "other", and discussed briefly. The most relevant disease-modifying candidates in PD are classified into the aforementioned categories and reviewed. Finally, conclusions and recommendations for future improvements in the field of disease modification in PD are provided.

Keywords: Clinical trials; Disease modification; Neuroprotection; Parkinson disease; Pathophysiology; Therapy

Key Summary Points

Disease modification in Parkinson disease (PD) remains an elusive goal, mainly due to the lack of established biomarkers of disease progression.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-025-00793-z.

C. Gonzalez-Robles (✉)
Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology, London WC1N 3BG, UK
e-mail: cristina.robles@ucl.ac.uk

O. Bandmann
Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield S10 2HQ, UK

O. Bandmann
Neuroscience Institute, University of Sheffield, Sheffield S10 2HQ, UK

A. H. V. Schapira
Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology, Royal Free Campus, London NW3 2PF, UK

Pathophysiological mechanisms in PD can be broadly classified into mitochondrial dysfunction, lysosomal dysfunction, inflammation, protein aggregation/propagation, and other (e.g. alterations in calcium signalling, insulin resistance).

Compounds aimed at one or various of the above mechanisms have been developed and tested in PD, with no positive phase 3 clinical trials so far.

Future improvements in preclinical research—PD animal models, PD classification (biological staging), trial participant selection (deep phenotyping and PD subtyping), outcome measures (tracking of progression), and trial design (novel designs such as platform trials)—are warranted to ensure progress in the discovery of disease-modifying interventions in PD.

INTRODUCTION

Parkinson disease (PD) is a relentlessly progressive neurodegenerative condition classically defined by bradykinesia and either rest tremor, rigidity, or both, but which also encompasses other motor (e.g. dysarthria, impairment of postural reflexes) and non-motor manifestations (e.g. hyposmia, cognitive decline, constipation, sleep disturbances) [1].

Since its original description by James Parkinson in 1817 [2], remarkable progress has been made in the symptomatic management of PD, from the discovery of levodopa in the late 1960s [3] to current advanced therapies, such as deep brain stimulation and magnetic resonance imaging (MRI)-guided focused ultrasound [4]. However, disease modification in PD remains an elusive goal, and none of the interventions trialled so far have shown a clinically proven neuroprotective effect.

This review aims to provide a brief overview of relevant concepts in disease modification, pathophysiological mechanisms in PD, the most relevant disease-modifying candidates so far, and challenges in neuroprotection in manifest PD, as well as to discuss strategies to address those. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

It is outside the scope of this work to review extensively *all* current neuroprotective trials and compounds in PD, and the reader is directed to recent publications on this topic [5–7]. Similarly, gene and cell therapies are beyond the purpose of this review and have been discussed in other recent publications [8, 9].

Discussions on disease modification in prodromal PD [10], which is also not covered in this review, might be premature at this stage, given the current status of this endeavour in manifest PD and the additional challenges which it entails. Nevertheless, progress in the field of manifest PD will hopefully aid its development, and two recent publications discuss strategies for PD prevention through lifestyle changes [11] and pharmacological interventions [12]. Trial design for PD prevention has also been recently reviewed [13].

Disease Modification: Relevant Concepts

In PD, disease-modifying therapies (DMTs) are defined as those which alter the course of the condition. This concept is well established in other fields, such as rheumatoid arthritis (RA) and multiple sclerosis (MS), which have robust biomarkers of disease progression—X-ray imaging and inflammatory markers (e.g. C-reactive protein) in RA, magnetic resonance imaging (MRI) in MS—and a wealth of DMTs [14, 15]. Unlike those examples, there is no established objective biomarker of disease progression for PD to date. Alpha-synuclein seed amplification assays have emerged recently as a promising diagnostic biomarker in PD and led to a shift in its classification towards a biological staging system [16–21]. However, their potential to track disease progression is still to be elucidated and may likely be limited.

Additional concepts in PD include *neuroprotection* (the prevention of neuronal cell death other than the expected age-related loss, with the consequent halt in disease progression),

neurorescue (salvaging of damaged neurons at risk of death) [22], *compensation* (enhancing defective compensatory mechanisms for dopaminergic neuronal cell death) [23], and *neurorestoration* (replacement of lost neurons via cell therapy) [24]. As with disease modification, there is currently no established biomarker to ascertain or measure those phenomena in PD.

Regarding PD pathogenesis, the systemic manifestations of PD prompted research into its mechanisms beyond the substantia nigra. Pathological and clinical findings in the early 2000s, namely the discovery of alpha-synuclein deposits in the olfactory bulb and dorsal motor nucleus of the vagus and the relatively frequent existence of gastrointestinal symptoms before onset of motor symptoms in PD, laid the foundations for the brain-first versus body-first hypothesis [25–27] and the dual-hit hypothesis [28]. However, recent publications suggest the possible coexistence of both as PD subtypes (*brain first* and *body-first*), each of them with a distinct phenotype [29, 30]. The *gut–brain* hypothesis also gave rise to research on the role of gut microbiota in PD [31, 32].

In terms of drug discovery, the lack of an optimal preclinical model in PD which faithfully resembles in vivo pathophysiology is one of its main limiting factors. Nevertheless, some models are more robust than others, and particular models may be of interest when testing compounds with specific mechanisms of action. Excellent reviews of preclinical PD models have been published recently [33–35].

Trial design plays a crucial role in clinical research, and different putative DMTs may benefit from specific designs, but overall, the traditional two-arm clinical trial design has proven inefficient. Subsequently, alternative designs—washout [36, 37], delayed start [38, 39], basket [40]—have been tested in PD. Adaptive designs, such as multi-arm, multi-stage (MAMS) trials, allow for sustained infrastructure and high throughput of putative DMTs and testing of exploratory outcomes, with a reduced proportion of participants being allocated to placebo [41]. MAMS trials have shown promise in other neurological conditions—MS [42], motor neuron disease [43]—and a phase 3 trial of putative DMTs in PD is currently under development in the UK [41].

Participant selection is an essential factor when testing putative DMTs in PD, especially considering its remarkable heterogeneity [44–47]. This will largely depend on the target population—idiopathic PD versus specific phenotypes/genotypes—but in general, an inclusive approach would be desirable—age, sex, ethnicity—complemented by enrichment of specific treatment arms according to the compounds' mode of action, to progress towards precision medicine [48, 49].

Despite the lack of a single established biomarker of disease progression in PD, recommendations on outcome measures for trials of DMT in PD have been published [50], with the aim of helping homogenise clinical research in PD, thus enhancing comparability of trial results.

A review of recent advances in the development and clinical assessment of putative neuroprotective compounds for the clinically and aetiology related but distinct alpha-synucleinopathy multiple system atrophy (MSA) is beyond the scope of this review. We direct the reader to recently published reviews on this topic [51, 52].

PATHOPHYSIOLOGY OF PARKINSON DISEASE

Supplementary Table 1 and Fig. 1 present an overview of pathogenetic mechanisms in PD. The most popular hypothesis is that sporadic PD is due to an interplay between genetic and environmental aetiological factors, which in turn lead to alterations in the mitochondrial, lysosomal, and inflammatory pathways, among others, leading to eventual neuronal cell death.

DISEASE-MODIFYING APPROACHES IN PARKINSON DISEASE

This section provides an overview of disease modification efforts in PD to date, which have frequently focused on the pathways described in Supplementary Table 1. It is important to note

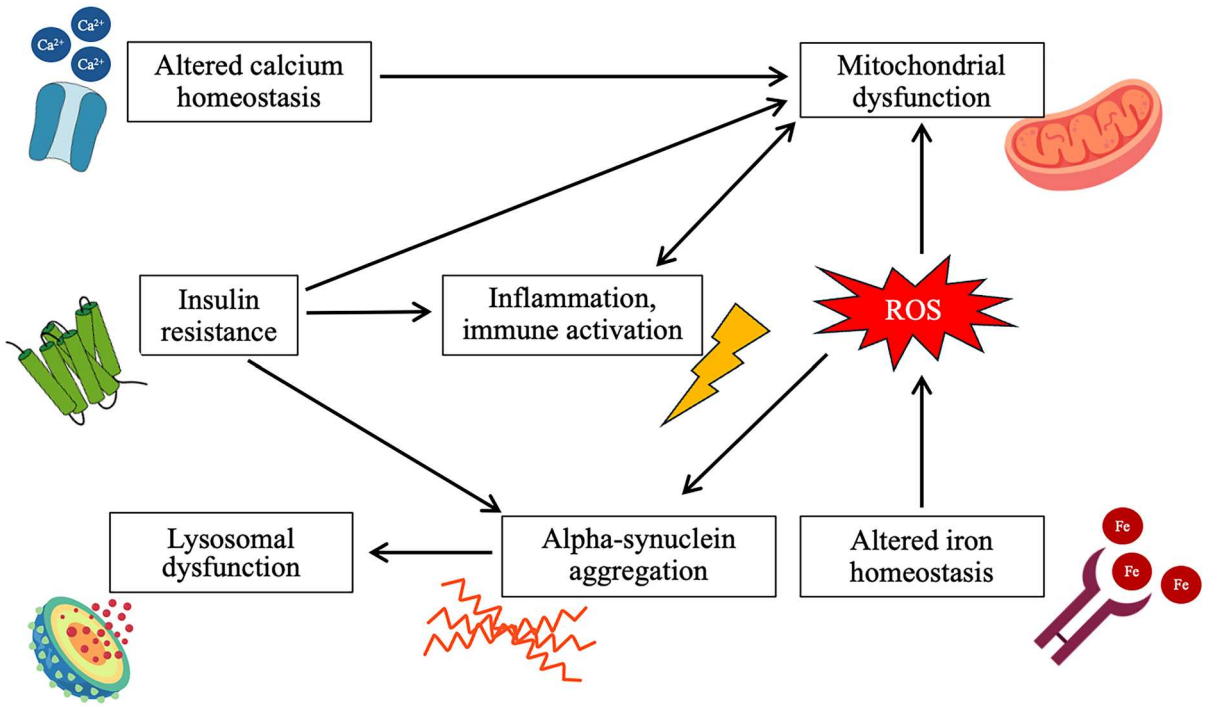

Fig. 1 Summary of pathogenetic mechanisms in Parkinson disease. *ROS* reactive oxygen species

that, given the heterogeneity of PD, some of the approaches may only benefit specific patients, such as those with genetic forms of PD. For a detailed account of current clinical trials in PD, we direct the reader to the 2024 edition of an excellent annual review by McFarthing et al. [6].

Mitochondrial

Quinones

Coenzyme Q10 (CoQ10) is a benzoquinone which increases tyrosine hydroxylase levels and reduces oxidative stress [53], inflammation, and apoptosis [54, 55].

Several clinical trials of CoQ10 in PD have been completed [56], proving its safety and tolerability but failing to show superiority versus placebo according to meta-analysis results [57, 58]. A phase 2 clinical trial of CoQ10 in PD stratifying participants according to "mitochondrial risk burden" via an omics-based approach is underway [59].

More recently, mitoquinone (MitoQ), another CoQ10 analogue and a potent antioxidant with positive preclinical evidence [60, 61], failed to demonstrate an effect on PD progression in a phase 2 clinical trial [62].

Idebenone, a synthetic CoQ10 analogue with antioxidant [63, 64] and mitophagy-regulating properties [65], is currently being tested in a phase 2 trial in individuals with prodromal PD (rapid eye movement [REM] sleep behaviour disorder [RBD]) (NCT04152655).

Creatine

Creatine is a nutritional supplement which enhances mitochondrial energy production [66] and has shown protective effects on preclinical PD models [67].

Despite overcoming futility analyses in a phase 2 trial [68–70], a phase 3 trial of creatinine monohydrate over 5 years in patients with PD on dopaminergic treatment yielded negative results [71].

Nicotinamide Riboside

Nicotinamide riboside (NR) is a precursor of nicotinamide adenine dinucleotide, which enhances mitochondrial function through various pathways [72].

After encouraging phase 1 evidence [73]—safety, tolerability, imaging, wet biomarkers, and clinical measures—and confirmation of its safety at high doses (3000 mg/day) in PD [74], a proof-of-concept study (NCT03568968) and a dose-optimisation study (NCT05589766) of NR are currently underway.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid licensed in the UK for the treatment of primary biliary cholangitis, dissolution of gallstones, and gall reflux gastritis [75]. Both UDCA and its taurine conjugate, tauroursodeoxycholic acid, have shown mitochondrial-enhancing, antioxidant, anti-inflammatory, and antiapoptotic effects in different preclinical PD models [76–83], as well as rescue of mitochondrial function in fibroblasts of people with PD [48, 84, 85].

Positive results from a pilot study [86] prompted a phase 2 trial of UDCA in PD, which confirmed its safety, tolerability, target engagement measured via 31-phosphorus magnetic resonance spectroscopy (31P-MRS), and reported gait improvement in the objective sensor-based analysis. No differences were found in part III (motor examination) of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), but this trial was not powered to detect such differences [87].

Terazosin

Terazosin is an alpha-1 adrenergic receptor antagonist licensed for the treatment of mild to moderate hypertension and benign prostatic hyperplasia [88]. Interestingly, it activates phosphoglycerate kinase 1, the first adenosine triphosphate (ATP)-generating enzyme in glycolysis, thus improving mitochondrial function in neurons [89–91]. Epidemiological evidence suggests a decrease in PD incidence [90, 91] as well as slower disease progression and fewer PD-related complications among individuals taking terazosin [90, 92, 93]. However, it has been suggested that the latter is due to an acceleration in PD disease progression among individuals taking tamsulosin, its comparator drug in some epidemiological studies [94].

Regarding its clinical evidence, a placebo-controlled 12-week pilot trial demonstrated target engagement measured via 31P-MRS and a significant increase in blood ATP levels with terazosin [95]. Two phase 2 trials are currently assessing its effects in prodromal PD (idiopathic RBD) (NCT04386317) and in pre-motor PD (NCT05109364), respectively.

Alpha-synuclein

Akin to the approach in Alzheimer disease (AD), PD research has explored removal of pathological alpha-synuclein aggregates as a disease-modifying strategy. Strategies for alpha-synuclein reduction have been reviewed recently, and include immunisation (active, passive), reduction of its expression (via small interfering ribonucleic acids and antisense oligonucleotides [ASOs], among other techniques), inhibition of its aggregation, and enhancement of its degradation [96]. Of those, immunisation and inhibition of aggregation are arguably the most widely assessed approaches in clinical trials.

Passive Immunisation

Cinpanemab (BIIB054), a human-derived monoclonal antibody which preferentially binds extracellular aggregated alpha-synuclein, failed to meet any primary and secondary endpoints over 52 weeks in a phase 2 trial [97], despite having shown safety, tolerability, and favourable pharmacokinetics in a previous phase 1 trial [98].

Prasinezumab (RO7046015/PRX002), a humanised monoclonal antibody which binds to aggregated alpha-synuclein at its C-terminal, also failed to show significant changes in clinical and imaging measures of disease progression versus placebo [99], although post hoc analyses

suggest a potential effect on rapidly progressing early PD [100].

Active Immunisation

ACI-7104.056, an adjuvanted protein peptide conjugate vaccine, is currently under investigation at different doses in a phase 2 placebo-controlled trial (NCT06015841), with positive interim results reported by the company in November 2024 [101] but no peer-reviewed publication yet.

UB-312, an active immunotherapeutic agent against alpha-synuclein, met its primary endpoints of safety, tolerability and immunogenicity in a phase 1 study [102].

Suppression of Alpha-Synuclein Messenger Ribonucleic Acid (mRNA) Translation

Buntanetap (also known as Posiphen or ANVS401) is an orally bioavailable small molecule which suppresses the translation of the mRNAs of multiple proteins, including alpha-synuclein. It is therefore hypothesised to restore proteostasis and halt neurodegeneration, and this is supported by data from animal studies [103–106]. This compound demonstrated safety and positive clinical and biomarker results in a phase 1/2 clinical trial in patients with early PD and in patients with early AD [107]. Subsequently, a phase 3 trial in the same population (NCT04524351) concluded in December 2023 and a peer-reviewed publication of results is pending, but the company (Annovis) reported significantly better motor outcomes—MDS-UPDRS part II, III, II + III total score—versus placebo in patients diagnosed over 3 years before enrolment and in patients with a postural instability and gait difficulty phenotype, as well as a halting in cognitive decline as measured by the Mini-Mental State Examination (MMSE) both in the entire PD cohort and in participants with mild dementia (MMSE scores between 20 and 26 [108]).

Inhibition of Alpha-Synuclein Aggregation

MT101-5, an oral standardised herbal formula which inhibits alpha-synuclein fibril formation [109], completed a phase 1 trial in 2023 (NCT05844787) with no published results, and a phase 2 trial is due to start in 2025 (NCT06175767).

A proof-of-concept phase 2a trial of oral Minzasolmin (UCB0599) (NCT04658186), an oral alpha-synuclein misfolding inhibitor [110], did not meet primary or secondary clinical endpoints according to a recent press release by its pharmaceutical company.

POD01A, a short peptide formulation targeted against oligomeric alpha-synuclein, was safe and well tolerated in a phase 1 study and resulted in a substantial humoral immune response [111].

Another oral alpha-synuclein aggregation inhibitor, Anle138b [112], showed favourable safety and pharmacokinetics in a phase 1 trial (NCT04208152) [113].

KM-819 is a novel compound which inhibits Fas-associated factor 1, a protein known to enhance alpha-synuclein accumulation and autophagy dysregulation [114]. A first-in-human study of the safety and pharmacokinetics of KM-819 reported positive results [115], and a phase 2 trial is currently ongoing (NCT05670782).

Lysosomal

Leucine-Rich Repeat Kinase 2 (LRRK2)-Targeting Therapies

LRRK2 is a ubiquitous protein whose physiological functions, although not yet fully elucidated, are known to involve mitochondrial function and inflammation [116, 117]. Interestingly, the role of LRRK2 in the endolysosomal system is becoming increasingly clear, which is further supported by its interaction with the beta-glucosidase 1 (GBA1) gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase) [117, 118].

Broadly, three strategies have been devised to target LRRK2: kinase inhibitors, ASOs, and guanosine triphosphate hydrolase (GTPase) modulators [119]. Of those, there is an ongoing phase 1 trial of the ASO BIIB094 (NCT03976349), and encouraging phase 1 and 1b results of kinase inhibitors DNL201 [120] and DNL151 [121]

prompted a phase 2 (NCT05348785) and a phase 3 (NCT05418673) trial on the latter.

GBA1-Targeting Therapies

GBA1-targeting therapies can be divided into substrate-reducing compounds, chaperones, GCase activators, and gene therapies [122].

Ambroxol, a repurposed cough medication which acts as an inhibitory chaperone aiding transfer of GCase into the lysosome, was safe and showed target engagement and central nervous system (CNS) penetration in patients with and without GBA1 mutations in a phase 2 clinical trial [123]. Consequently, a phase 3 trial on ambroxol has been planned and is due to start recruitment in the near future (NCT05778617), a phase 2 trial in GBA-associated PD is ongoing (NCT05287503) [124], and another phase 2 trial on PD dementia is expected to finish in December 2025 (NCT02914366) [125].

Conversely, venglustat, a glucosylceramide synthase inhibitor, failed to show any clinical benefit over placebo in GBA1-related PD in part 2 of a recent phase 2 trial [126], after having demonstrated favourable safety, tolerability, and target engagement in the cerebrospinal fluid (CSF) in part 1 of the same trial [127].

Additionally, a phase 1/2a trial of intracisternal PR001/LY3884961, a viral vector (AAV9) containing wild type GBA1 to restore GCase activity in patients with PD with at least one GBA1 mutation, is currently underway (NCT04127578).

Inflammation

Non-steroidal Anti-inflammatory Drugs (NSAIDs): Ibuprofen

Preclinical studies have shown anti-inflammatory and antioxidant effects of ibuprofen in PD [128–131, 131–133]. Moreover, epidemiological studies have reported a reduction in PD risk among ibuprofen [134–137] and non-aspirin NSAID [138] users, both in the general population and among carriers of LRRK2 risk variants [139], although other studies have failed to confirm this association [140, 141]. Despite the above, to the authors' knowledge, there are no ongoing or completed clinical trials of ibuprofen as a potential DMT in PD.

Statins

Statins are a group of compounds licensed as lipid-lowering therapies. Preclinical studies have reported effects on inflammation, oxidative stress, apoptosis, and alpha-synuclein aggregation [142]. However, there is conflicting epidemiological evidence on statins and PD risk [143].

Regarding clinical evidence, lovastatin was well tolerated and showed a non-significant trend towards less motor symptom worsening and significantly less deterioration in positron emission tomography (PET) imaging versus placebo in a phase 2 trial in an early PD cohort [144]. Nevertheless, a more recent placebo-controlled futility trial of simvastatin in moderate PD failed to meet its primary endpoint [145].

Immunosuppressants

Immunosuppressants have been successful at protecting dopaminergic neurons against neurodegeneration, reducing microglial activation and motor progression in PD preclinical models.

For four decades, azathioprine (AZA) has been used as an immunosuppressive and anti-inflammatory agent in organ transplantation (kidney and heart) [64, 65] and in chronic inflammatory diseases, including MS [66–73]. AZA is a prodrug selectively converted to the purine analogue 6-mercaptopurine in target cells, and purine nucleotide biosynthesis inhibition and downregulation of B and T cell function have been suggested as its main mechanism of action [74–78]. Furthermore, AZA (and its metabolites) can induce apoptosis of T cells through cluster of differentiation-28 (CD28) co-stimulation, mediated by a specific binding of azathioprine-generated 6-thioguanine triphosphate to Ras-related C3 botulinum toxin substrate 1 (Rac1) instead of GTP, converting a co-stimulatory into an apoptotic signal. 6-Thio-GTP derivates, therefore, exert their immunosuppressive activity at least in part through slow but quite selective mechanisms [79].

Azathioprine, a purine analogue [146, 147, 147] with various indications (e.g. MS) is

currently being tested in a phase 2 trial which aims to detect disease modification and target engagement both centrally (PET imaging, CSF immune markers) and peripherally (blood immune markers) in an early PD cohort with high risk of disease progression [148].

Sargramostim is a human recombinant granulocyte–macrophage colony-stimulating factor which has shown preclinical evidence of protection against nigrostriatal degeneration [149, 150]. A phase 1 trial in patients with PD and controls demonstrated good tolerability, improvement in serum immune markers, and a modest motor improvement [151]. A 33-month open-label study also showed long-term safety and effects on immune profile, as well as stability in motor scores of the Unified Parkinson's Disease Rating Scale (UPDRS) [152].

Neflamapimod is a p38-alpha inhibitor with anti-inflammatory effects [153] which also intervenes in endocytosis and basal forebrain cholinergic neuron (BFCN) degeneration [154]. After its promising effects on biomarkers in a phase 2 trial on AD [155], a phase 2a study in patients with mild-to-moderate dementia with Lewy bodies (DLB) showed a favourable safety profile as well as reversal of pathology in a BFCN degeneration mouse model [154]. Targeting BFCN degeneration may also improve gait in PD, given previous evidence in this field [156, 157].

Other Approaches

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 receptor agonists exert effects in different pathophysiological PD pathways: inflammation [158], alpha-synuclein aggregation [159], and, importantly, mitochondrial function, enhancing antioxidant processes and mitochondrial biogenesis [160]. Exenatide, and in particular its extended-release (ER) formulation, is the GLP-1 receptor agonist with the broadest clinical evidence, including motor and cognitive improvements in an open-label phase 2 study [161] which persisted 12 months after drug withdrawal [162], as well as motor improvement in a placebo-controlled phase 2 trial [163]. A secondary analysis of that trial confirmed target engagement of exenatide (brain insulin, Akt [protein kinase B] and mammalian target of rapamycin [mTOR] signalling pathways) as measured on neuronal extracellular vesicles, with some of the observed changes correlating with motor outcomes [164]. The results of a phase 3 trial of exenatide ER [165] have been published recently, indicating that there was no benefit across a range of primary and secondary endpoints [166]. This prompts several questions, both regarding the disease-modifying potential of other GLP-1 agonists, especially dual agonists (e.g. tirzepatide), and in regard to the target population, specifically whether patients with PD and insulin resistance may benefit from these agents.

A phase 2 trial on pegylated exenatide (NLY01) was negative for motor and non-motor measures, with subgroup analysis suggesting potential motor benefit in younger individuals [167]; and a phase 2 trial on sustained-release exenatide (PT320) has not published its results yet (NCT04269642).

Regarding other GLP-1 agonists, a recent phase 2 trial of lixisenatide showed significantly reduced motor progression over 12 months and lower motor scores after washout, at 14 months [168].

Furthermore, a phase 2 study of semaglutide is not yet recruiting (NCT03659682), and a phase 2 trial of liraglutide demonstrated improvement in non-motor symptoms and activities of daily living (ADL) but failed to show significant differences in motor and cognitive status versus placebo [169].

Calcium Channel Blockers: Isradipine and Zonisamide

Blockade of calcium channels can protect dopaminergic neurons against oxidative damage and iron accumulation [170–176]. Additionally, the L-type Cav1.3 channel plays a role in dopamine D2-autoreceptor desensitisation, which may drive adaptation of dopaminergic neuronal activity in response to extracellular dopamine levels [177].

Epidemiological evidence has shown a reduction in PD risk among long-term users of calcium channel blockers [178–180].

Isradipine is a dihydropyridine calcium channel blocker commonly used as an antihypertensive agent [181, 182]. After a positive phase 2 trial testing isradipine ER at different doses, a phase 3 trial of isradipine immediate-release 5 mg twice daily did not meet its endpoints [183]. The authors re-analysed the data from the phase 2 trial and concluded that the ER formulation may be more effective in achieving target engagement, therefore proposing a longer study with higher doses (i.e. isradipine ER 10 mg) [184].

Zonisamide is a T-type calcium channel blocker antiepileptic, also approved in Japan for the treatment of motor symptoms as an adjunct to levodopa in PD and DLB [185–187].

Besides its symptomatic effect, a number of preclinical studies have reported its disease-modifying potential [188–193]. A retrospective cohort study on patients with PD taking zonisamide in addition to levodopa reported a delay in progression as measured by dopamine transporter single-photon emission computed tomography as well as clinical improvement [194]. Another cohort study on patients with PD found zonisamide to be associated with a lower risk of dementia, insomnia, and gastric ulcers than three other antiparkinsonian medications [195]. An open-label study reported reduced inflammatory activity as measured by PET as well as enhanced attention scores in the zonisamide group [196].

Monoamine Oxidase B (MAO-B) Inhibitors

Rasagiline is a MAO-B inhibitor approved for the treatment of PD symptoms which has shown neuroprotective potential in preclinical studies [197–201]. A 72-week double-blind, placebo-controlled, delayed-start trial of rasagiline 1 mg or 2 mg in PD reported a reduction in motor progression as measured by the UPDRS score in the 1 mg group versus placebo, but the 2 mg group did not meet any prespecified endpoints [202]. This raised questions about the study design and led the authors to recommend caution when interpreting the results. Post hoc analyses from that trial showed additional significant differences in the ADL part of the UPDRS as well as a delay in the start of dopaminergic therapy in the rasagiline 1 mg early-start group versus the delayed-start group [39]. Nevertheless, a 3-year open-label follow-up study failed to show long-term benefits of rasagiline in PD progression [203]. Despite these results, a phase 2/3 trial is currently evaluating the potential of rasagiline to reduce the progression from idiopathic RBD to PD (NCT05611372).

Beta-adrenoreceptor agonists: Salbutamol/Albuterol

Adrenergic agonists have been reported to regulate alpha-synuclein deposition, inflammation, and alpha-synuclein (SNCA) gene expression in preclinical PD models [204]. Salbutamol, licensed in the UK for the treatment of asthma and bronchospasm [205], was associated with a decreased risk of parkinsonism in a large self-controlled cohort study [180] and in two longitudinal incident PD cohorts [206], although another study failed to show this association [207]. Several open-label studies have reported a symptomatic benefit of salbutamol as add-on therapy to levodopa in PD [208–210], and it is currently being tested in an ongoing phase 2 parallel-group disease-modifying PD trial [211].

Iron Chelators: Deferiprone

Excess iron in the CNS leads to increased oxidative stress, and therefore its removal has been postulated as a neuroprotective strategy in PD [212].

Deferiprone, an iron chelator licensed in the UK for the treatment of thalassaemia major [213], showed clinical and radiological benefit over placebo in a delayed-start trial in early PD [214], and the radiological changes were confirmed in a subsequent phase 2 placebo-controlled trial [215]. Nevertheless, a larger phase 2 placebo-controlled trial in early untreated PD showed significant clinical worsening in the deferiprone group, despite reduction of brain iron levels in MRI [216].

Non-pharmacological Interventions:

Exercise

A growing body of preclinical and clinical evidence supports the benefits of exercise in PD: epidemiological studies have found a reduced risk of PD among healthy individuals who are more physically active [217], as well as an improvement in off-medication gait parameters [218] and a delay in the progression of some PD signs and symptoms [219] and reduced mortality in physically active patients with PD [220]. Furthermore, an extensive review concluded that sustained physical exercise is beneficial for people with PD in the long term [221]. A recent symptomatic double-blind randomised controlled trial of aerobic exercise in PD reported an improvement in off symptoms [222]. As a result, several studies exploring the disease-modifying potential of exercise in PD are ongoing (NCT04284436), some of them including smartphone-based apps [223, 224].

For more information, the readers are directed to a recent excellent review on clinical trials of aerobic exercise in PD [225].

CONCLUSION

Neuroprotection in PD remains a challenging but urgently important goal. Regarding preclinical studies, animal and cell models are useful to help understand PD pathophysiology and to increase the chances of clinical success of putative DMT, and patient-derived tissues probably represent a valuable source of information in this setting.

From a clinical point of view, functionally relevant, "dopa-refractory" clinical outcome measures are needed in disease-modifying PD clinical trials, ideally combined with promising exploratory endpoints, such as digital health technologies, wet biomarkers, and imaging techniques, for patient stratification, confirmation of target engagement, and tracking of disease progression.

These strategies, alongside innovative trial designs such as MAMS platform trials, and consideration of repurposed compounds as well as novel agents, will hopefully accelerate the discovery of disease-modifying agents in PD—a goal which has been already achieved in other neurological conditions, such as MS—ultimately to improve the prognosis and quality of life of people with PD regardless of their clinical and biological subtype, stage, and symptomatic treatment status.

Author Contributions. Cristina Gonzalez-Robles: conception and writing of the first draft. Oliver Bandmann: conception and editing of draft versions of the manuscript, writing and editing of the final version of the manuscript. Anthony HV Schapira: conception and editing of draft versions of the manuscript, writing and editing of the final version of the manuscript.

Funding. No funding or sponsorship was received for the publication of this article. The UCL Queen Square Movement Disorders Centre (Anthony HV Schapira) acknowledge funding from the UCLH Biomedical Research Centre for this study.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Cristina Gonzalez-Robles has received research support from the Edmond J. Safra (EJS) Foundation (EJS Accelerating Clinical Trials in Parkinson's Disease (EJS ACT-PD) project). Oliver Bandmann has received grants from Cure Parkinson's (OB02), the Medical Research Council (MRC)—Centre of Excellence Award (CoEN) (MR/V006525/1) and the Jon Moulton Charity Trust. He has served on the Advisory Board for ICE. Anthony HV Schapira has received grants from the MRC (UK), Cure Parkinson's Trust, Parkinson's UK, EU H2020 program and Aligning Science Against

Parkinson's (ASAP), MJFF, Innovate UK and consults for Capsida and Neurocrine. Anthony HV Schapira is an Editorial Board member of Neurology and Therapy. Anthony HV Schapira was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386(9996):896–912.
2. Parkinson J. An essay on the shaking palsy. J Neuropsychiatry Clin Neurosci. 2002;14(2):223–36.
3. Abbott A. Levodopa: the story so far. Nature. 2010;466(7310):S6-7.
4. Serva SN, Bernstein J, Thompson JA, Kern DS, Ojemann SG. An update on advanced therapies for Parkinson's disease: from gene therapy to neuromodulation. Front Surg. 2022;23(9): 863921.
5. Vijiaratnam N, Simuni T, Bandmann O, Morris HR, Foltynie T. Progress towards therapies for disease modification in Parkinson's disease. Lancet Neurol. 2021;20(7):559–72.
6. McFarthing K, Buff S, Rafaloff G, Pitzer K, Fiske B, Navangul A, et al. Parkinson's disease drug therapies in the clinical trial pipeline: 2024 update. J Parkinson's Dis. 2024;14(5):899–912.
7. Kalia LV, Asis A, Arbour N, Bar-Or A, Bove R, Di Luca DG, et al. Disease-modifying therapies for Parkinson disease: lessons from multiple sclerosis. Nat Rev Neurol. 2024;20(12):724–37.
8. Barker RA, Björklund A. Restorative cell and gene therapies for Parkinson's disease. In: Handbook of clinical neurology [Internet]. Elsevier; 2023. p. 211–26. https://linkinghub.elsevier.com/retrieve/pii/B9780323855556000126. Accessed 28 Jan 2025.
9. Grote J, Patel N, Bates C, Parmar MS. From lab bench to hope: a review of gene therapies in clinical trials for Parkinson's disease and challenges. Neurol Sci. 2024;45(10):4699–710.
10. Salat D, Noyce AJ, Schrag A, Tolosa E. Challenges of modifying disease progression in prediagnostic Parkinson's disease. Lancet Neurol. 2016;15(6):637–48.
11. Janssen Daalen JM, Schootemeijer S, Richard E, Darweesh SKL, Bloem BR. Lifestyle interventions for the prevention of parkinson disease: a recipe for action. Neurology. 2022;99(7_Supplement_1):42–51.
12. Crotty GF, Schwarzschild MA. What to test in parkinson disease prevention trials? Repurposed, low-risk, and gene-targeted drugs. Neurology. 2022;99(7_Supplement_1):34–41.
13. Crotty GF, Ayer SJ, Schwarzschild MA. Designing the first trials for Parkinson's prevention. Berg D, Bloem BR, Kalia LV, Postuma RB, editors. J Parkinson's Dis. 2024;14(s2):S381–93.
14. Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. Lancet. 2023;402(10416):2019–33.
15. Dalla Costa G, Leocani L, Rodegher M, Chiveri L, Gradassi A, Comi G. An overview on disease modifying and symptomatic drug treatments for multiple sclerosis. Expert Rev Clin Pharmacol. 2024;17(10):901–21.
16. Concha-Marambio L, Pritzkow S, Shahnawaz M, Farris CM, Soto C. Seed amplification assay for the detection of pathologic alpha-synuclein aggregates in cerebrospinal fluid. Nat Protoc. 2023;18(4):1179–96.
17. Okuzumi A, Hatano T, Matsumoto G, Nojiri S, Ueno S, Imamichi-Tatano Y, et al. Propagative α-synuclein seeds as serum biomarkers for synucleinopathies. Nat Med. 2023;29(6):1448–55.

18. Siderowf A, Concha-Marambio L, Lafontant DE, Farris CM, Ma Y, Urenia PA, et al. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study. Lancet Neurol. 2023;22(5):407–17.

19. Simuni T, Chahine LM, Poston K, Brumm M, Buracchio T, Campbell M, et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. Lancet Neurol. 2024;23(2):178–90.

20. Höglinger GU, Adler CH, Berg D, Klein C, Outeiro TF, Poewe W, et al. A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria. Lancet Neurol. 2024;23(2):191–204.

21. Höglinger GU, Lang AE. The why and how of the SynNerGe criteria of Parkinson's disease. J Neural Transm. 2024;131(10):1149–54.

22. Schapira AHV. Science, medicine, and the future: Parkinson's disease. BMJ. 1999;318(7179):311–4.

23. Blesa J, Trigo-Damas I, Dileone M, Del Rey NLG, Hernandez LF, Obeso JA. Compensatory mechanisms in Parkinson's disease: circuits adaptations and role in disease modification. Exp Neurol. 2017;298:148–61.

24. Lang AE, Espay AJ. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. Mov Disord. 2018;33(5):660–77.

25. Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm. 2003;110(5):517–36.

26. Braak H, Tredici KD, Rüb U, De Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197–211.

27. Braak H, De Vos RAI, Bohl J, Del Tredici K. Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. Neurosci Lett. 2006;396(1):67–72.

28. Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. Neuropathol Appl Neurobio. 2007;33(6):599–614.

29. Borghammer P, Van Den Berge N. Brain-first versus gut-first Parkinson's disease: a hypothesis. Van Laar T, editor. J Parkinson's Dis. 2019;9(s2):S281–95.

30. Borghammer P. The brain-first vs. body-first model of Parkinson's disease with comparison to alternative models. J Neural Transm. 2023;130(6):737–53.

31. Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. Lancet Neurol. 2020;19(2):179–94.

32. Menozzi E, Macnaughtan J, Schapira AHV. The gut-brain axis and Parkinson disease: clinical and pathogenetic relevance. Ann Med. 2021;53(1):611–25.

33. Lama J, Buhidma Y, Fletcher EJR, Duty S. Animal models of Parkinson's disease: a guide to selecting the optimal model for your research. Neuronal Signal. 2021;5(4):NS20210026.

34. Ke M, Chong CM, Zhu Q, Zhang K, Cai CZ, Lu JH, et al. Comprehensive perspectives on experimental models for Parkinson's disease. Aging Dis. 2021;12(1):223.

35. Dovonou A, Bolduc C, Soto Linan V, Gora C, Peralta Iii MR, Lévesque M. Animal models of Parkinson's disease: bridging the gap between disease hallmarks and research questions. Transl Neurodegener. 2023;12(1):36.

36. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med. 1989;321:1364–71.

37. Ploeger BA, Holford NHG. Washout and delayed start designs for identifying disease modifying effects in slowly progressive diseases using disease progression analysis. Pharm Stat. 2009;8(3):225–38.

38. D'Agostino RB. The delayed-start study design. N Engl J Med. 2009;361(13):1304–6.

39. Rascol O, Fitzer-Attas CJ, Hauser R, Jankovic J, Lang A, Langston JW, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes. Lancet Neurol. 2011;10(5):415–23.

40. Cummings J, Montes A, Kamboj S, Cacho JF. The role of basket trials in drug development for neurodegenerative disorders. Alzheimer's Res Ther. 2022;14(1):73.

41. Foltynie T, Gandhi S, Gonzalez-Robles C, Zeissler ML, Mills G, Barker R, et al. Towards a multi-arm multi-stage platform trial of disease modifying approaches in Parkinson's disease. Brain. 2023;146(7):2717–22.

42. Li V, Leurent B, Barkhof F, Braisher M, Cafferty F, Ciccarelli O, et al. Designing multi-arm

multistage adaptive trials for neuroprotection in progressive multiple sclerosis. Neurology. 2022;98(18):754–64.

43. Wong C, Dakin RS, Williamson J, Newton J, Steven M, Colville S, et al. Motor neuron disease systematic multi-arm adaptive randomised trial (MND-SMART): a multi-arm, multi-stage, adaptive, platform, phase III randomised, double-blind, placebo-controlled trial of repurposed drugs in motor neuron disease. BMJ Open. 2022;12(7): e064173.

44. Espay AJ, Schwarzschild MA, Tanner CM, Fernandez HH, Simon DK, Leverenz JB, et al. Biomarker-driven phenotyping in Parkinson's disease: a translational missing link in disease-modifying clinical trials. Mov Disord. 2017;32(3):319–24.

45. Fereshtehnejad SM, Postuma RB. Subtypes of Parkinson's disease: what do they tell us about disease progression? Curr Neurol Neurosci Rep. 2017;17(4):34.

46. Brolin K, Bandres-Ciga S, Blauwendraat C, Widner H, Odin P, Hansson O, et al. Insights on genetic and environmental factors in Parkinson's disease from a regional swedish case–control cohort. JPD. 2022;12(1):153–71.

47. Dulski J, Uitti RJ, Beasley A, Hernandez D, Ramanan VK, Cahn EJ, et al. Genetics of Parkinson's disease heterogeneity: a genome-wide association study of clinical subtypes. Parkinsonism Relat Disord. 2024;119: 105935.

48. Carling PJ, Mortiboys H, Green C, Mihaylov S, Sandor C, Schwartzentruber A, et al. Deep phenotyping of peripheral tissue facilitates mechanistic disease stratification in sporadic Parkinson's disease. Prog Neurobiol. 2020;187: 101772.

49. D'Sa K, Evans JR, Virdi GS, Vecchi G, Adam A, Bertolli O, et al. Prediction of mechanistic subtypes of Parkinson's using patient-derived stem cell models. Nat Mach Intell. 2023;5(8):933–46.

50. Gonzalez-Robles C, Weil RS, Van Wamelen D, Bartlett M, Burnell M, Clarke CS, et al. Outcome measures for disease-modifying trials in Parkinson's disease: consensus paper by the EJS ACT-PD multi-arm multi-stage trial initiative. JPD. 2023;13(6):1011–33.

51. Bendetowicz D, Fabbri M, Sirna F, Fernagut PO, Foubert-Samier A, Saulnier T, et al. Recent advances in clinical trials in multiple system atrophy. Curr Neurol Neurosci Rep. 2024;24(4):95–112.

52. Krismer F, Fanciulli A, Meissner WG, Coon EA, Wenning GK. Multiple system atrophy: advances in pathophysiology, diagnosis, and treatment. Lancet Neurol. 2024;23(12):1252–66.

53. Magesh S, Chen Y, Hu L. Small molecule modulators of Keap1-Nrf2-ARE pathway as potential preventive and therapeutic agents. Med Res Rev. 2012;32(4):687–726.

54. Al-Megrin WA, Soliman D, Kassab RB, Metwally DM, Moneim AEA, El-Khadragy MF. Coenzyme Q10 activates the antioxidant machinery and inhibits the inflammatory and apoptotic cascades against lead acetate-induced renal injury in rats. Front Physiol. 2020;11:64.

55. Ghasemloo E, Mostafavi H, Hosseini M, Forouzandeh M, Eskandari M, Mousavi SS. Neuroprotective effects of coenzyme Q10 in Parkinson's model via a novel Q10/miR-149-5p/MMPs pathway. Metab Brain Dis. 2021;36(7):2089–100.

56. Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG. Coenzyme Q10 and Parkinsonian syndromes: a systematic review. JPM. 2022;12(6):975.

57. Negida A, Menshawy A, El Ashal G, Elfouly Y, Hani Y, Hegazy Y, et al. Coenzyme Q10 for patients with Parkinson's disease: a systematic review and meta-analysis. CNSNDDT. 2016;15(1):45–53.

58. Zhu ZG, Sun MX, Zhang WL, Wang WW, Jin YM, Xie CL. The efficacy and safety of coenzyme Q10 in Parkinson's disease: a meta-analysis of randomized controlled trials. Neurol Sci. 2017;38(2):215–24.

59. Prasuhn J, Brüggemann N, Hessler N, Berg D, Gasser T, Brockmann K, et al. An omics-based strategy using coenzyme Q10 in patients with Parkinson's disease: concept evaluation in a double-blind randomized placebo-controlled parallel group trial. Neurol Res Pract. 2019;1(1):31.

60. Ghosh A, Chandran K, Kalivendi SV, Joseph J, Antholine WE, Hillard CJ, et al. Neuroprotection by a mitochondria-targeted drug in a Parkinson's disease model. Free Radic Biol Med. 2010;49(11):1674–84.

61. Solesio ME, Prime TA, Logan A, Murphy MP, Del Mar Arroyo-Jimenez M, Jordán J, et al. The mitochondria-targeted anti-oxidant MitoQ reduces aspects of mitochondrial fission in the 6-OHDA cell model of Parkinson's disease. Biochim Biophys Acta (BBA) Mol Basis Dis. 2013;1832(1):174–82.

62. Snow BJ, Rolfe FL, Lockhart MM, Frampton CM, O'Sullivan JD, Fung V, 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. 2010;25(11):1670–4.

63. Montenegro L, Turnaturi R, Parenti C, Pasquinucci L. Idebenone: novel strategies to improve

its systemic and local efficacy. Nanomaterials. 2018;8(2):87.

64. Avcı B, Günaydın C, Güvenç T, Yavuz CK, Kuruca N, Bilge SS. Idebenone ameliorates rotenone-induced Parkinson's disease in rats through decreasing lipid peroxidation. Neurochem Res. 2021;46(3):513–22.

65. Yan J, Sun W, Shen M, Zhang Y, Jiang M, Liu A, et al. Idebenone improves motor dysfunction, learning and memory by regulating mitophagy in MPTP-treated mice. Cell Death Discov. 2022;8(1):28.

66. Tarnopolsky MA, Parshad A, Walzel B, Schlattner U, Wallimann T. Creatine transporter and mitochondrial creatine kinase protein content in myopathies. Muscle Nerve. 2001;24(5):682–8.

67. Matthews RT, Ferrante RJ, Klivenyi P, Yang L, Klein AM, Mueller G, et al. Creatine and cyclocreatine attenuate MPTP neurotoxicity. Exp Neurol. 1999;157(1):142–9.

68. The NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology. 2006;66(5):664–71.

69. The NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q_{10} and GPI-1485 in early Parkinson disease. Neurology. 2007;68(1):20–8.

70. NINDS NET-PD Investigators. A pilot clinical trial of creatine and minocycline in early Parkinson disease: 18-month results. Clin Neuropharmacol. 2008;31(3):141–50.

71. Kieburtz K, Tilley BC, Elm JJ, Babcock D, Hauser R, Ross GW, et al. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. JAMA. 2015;313(6):584.

72. Schöndorf DC, Ivanyuk D, Baden P, Sanchez-Martinez A, De Cicco S, Yu C, et al. The NAD+ precursor nicotinamide riboside rescues mitochondrial defects and neuronal loss in iPSC and fly models of Parkinson's disease. Cell Rep. 2018;23(10):2976–88.

73. Brakedal B, Dölle C, Riemer F, Ma Y, Nido GS, Skeie GO, et al. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. Cell Metab. 2022;34(3):396-407.e6.

74. Berven H, Kverneng S, Sheard E, Søgnen M, Af Geijerstam SA, Haugarvoll K, et al. NR-SAFE: a randomized, double-blind safety trial of high dose nicotinamide riboside in Parkinson's disease. Nat Commun. 2023;14(1):7793.

75. Joint Formulary Committee. Ursodeoxycholic acid. In: Joint Formulary Committee. British National Formulary. [BNF online]. London: BMJ Group and Pharmaceutical Press; 2025. https://bnf.nice.org.uk/drugs/ursodeoxycholic-acid/. Accessed 5 Mar 2025.

76. Castro-Caldas M, Carvalho AN, Rodrigues E, Henderson CJ, Wolf CR, Rodrigues CMP, et al. Tauroursodeoxycholic acid prevents MPTP-induced dopaminergic cell death in a mouse model of Parkinson's disease. Mol Neurobiol. 2012;46(2):475–86.

77. Chun HS, Low WC. Ursodeoxycholic acid suppresses mitochondria-dependent programmed cell death induced by sodium nitroprusside in SH-SY5Y cells. Toxicology. 2012;292(2–3):105–12.

78. Abdelkader NF, Safar MM, Salem HA. Ursodeoxycholic acid ameliorates apoptotic cascade in the rotenone model of Parkinson's disease: modulation of mitochondrial perturbations. Mol Neurobiol. 2016;53(2):810–7.

79. Moreira S, Fonseca I, Nunes MJ, Rosa A, Lemos L, Rodrigues E, et al. Nrf2 activation by tauroursodeoxycholic acid in experimental models of Parkinson's disease. Exp Neurol. 2017;295:77–87.

80. Rosa AI, Duarte-Silva S, Silva-Fernandes A, Nunes MJ, Carvalho AN, Rodrigues E, et al. Tauroursodeoxycholic acid improves motor symptoms in a mouse model of Parkinson's disease. Mol Neurobiol. 2018;55(12):9139–55.

81. Qi H, Shen D, Jiang C, Wang H, Chang M. Ursodeoxycholic acid protects dopaminergic neurons from oxidative stress via regulating mitochondrial function, autophagy, and apoptosis in MPTP/MPP+-induced Parkinson's disease. Neurosci Lett. 2021;741: 135493.

82. Huang F. Ursodeoxycholic acid as a potential alternative therapeutic approach for neurodegenerative disorders: effects on cell apoptosis, oxidative stress and inflammation in the brain. Brain Behav Immun Health. 2021;18: 100348.

83. Cuevas E, Burks S, Raymick J, Robinson B, Gómez-Crisóstomo NP, Escudero-Lourdes C, et al. Tauroursodeoxycholic acid (TUDCA) is neuroprotective in a chronic mouse model of Parkinson's disease. Nutr Neurosci. 2022;25(7):1374–91.

84. Mortiboys H, Aasly J, Bandmann O. Ursocholanic acid rescues mitochondrial function in common forms of familial Parkinson's disease. Brain. 2013;136(10):3038–50.

85. Mortiboys H, Furmston R, Bronstad G, Aasly J, Elliott C, Bandmann O. UDCA exerts beneficial effect on mitochondrial dysfunction in

LRRK2 ^{G2019S} carriers and in vivo. Neurology. 2015;85(10):846–52.

86. Sathe AG, Tuite P, Chen C, Ma Y, Chen W, Cloyd J, et al. Pharmacokinetics, safety, and tolerability of orally administered ursodeoxycholic acid in patients with Parkinson's disease—a pilot study. J Clin Pharma. 2020;60(6):744–50.

87. Payne T, Appleby M, Buckley E, Van Gelder LMA, Mullish BH, Sassani M, et al. A double-blind, randomized, placebo-controlled trial of ursodeoxycholic acid (UDCA) in Parkinson's disease. Mov Disord. 2023;38(8):1493–502.

88. Joint Formulary Committee. Terazosin. In: Joint Formulary Committee. British National Formulary. [BNF online]. London: BMJ Group and Pharmaceutical Press; 2025. https://bnf.nice.org.uk/drugs/terazosin/. Accessed 5 Mar 2025.

89. Chen X, Zhao C, Li X, Wang T, Li Y, Cao C, et al. Terazosin activates Pgk1 and Hsp90 to promote stress resistance. Nat Chem Biol. 2015;11(1):19–25.

90. Cai R, Zhang Y, Simmering JE, Schultz JL, Li Y, Fernandez-Carasa I, et al. Enhancing glycolysis attenuates Parkinson's disease progression in models and clinical databases. J Clin Investig. 2019;129(10):4539–49.

91. Simmering JE, Welsh MJ, Liu L, Narayanan NS, Pottegård A. Association of glycolysis-enhancing α-1 blockers with risk of developing parkinson disease. JAMA Neurol. 2021;78(4):407.

92. Weber MA, Sivakumar K, Tabakovic EE, Oya M, Aldridge GM, Zhang Q, et al. Glycolysis-enhancing α1-adrenergic antagonists modify cognitive symptoms related to Parkinson's disease. npj Parkinsons Dis. 2023;9(1):32.

93. Opheim KM, Uc EY, Cantrell MA, Lund BC. The impact of alpha-1-adrenergic receptor antagonists on the progression of Parkinson disease. J Am Pharm Assoc. 2024;64(2):437-443.e3.

94. Sasane R, Bartels A, Field M, Sierra MI, Duvvuri S, Gray DL, et al. Parkinson disease among patients treated for benign prostatic hyperplasia with α1 adrenergic receptor antagonists. J Clin Investig. 2021;131(11): e145112.

95. Schultz JL, Brinker AN, Xu J, Ernst SE, Tayyari F, Rauckhorst AJ, et al. A pilot to assess target engagement of terazosin in Parkinson's disease. Parkinsonism Relat Disord. 2022;94:79–83.

96. Grosso Jasutkar H, Oh SE, Mouradian MM. Therapeutics in the pipeline targeting α-synuclein for Parkinson's disease. Pharmacol Rev. 2022;74(1):207–37.

97. Lang AE, Siderowf AD, Macklin EA, Poewe W, Brooks DJ, Fernandez HH, et al. Trial of cinpanemab in early Parkinson's disease. N Engl J Med. 2022;387(5):408–20.

98. Brys M, Fanning L, Hung S, Ellenbogen A, Penner N, Yang M, et al. Randomized phase I clinical trial of anti–α-synuclein antibody BIIB054. Mov Disord. 2019;34(8):1154–63.

99. Pagano G, Taylor KI, Anzures-Cabrera J, Marchesi M, Simuni T, Marek K, et al. Trial of prasinezumab in early-stage Parkinson's disease. N Engl J Med. 2022;387(5):421–32.

100. Pagano G, Taylor KI, Anzures Cabrera J, Simuni T, Marek K, Postuma RB, et al. Prasinezumab slows motor progression in rapidly progressing early-stage Parkinson's disease. Nat Med. 2024;30(4):1096–103.

101. AC Immune. 'AC Immune Reports Positive Interim Results from Phase 2 Trial of ACI-7104.056 Active Immunotherapy in Early Parkinson's Disease'. Updated November 2024. In: https://ml-eu.globenewswire.com/Resource/Download/689a44f6-77e5-4a17-9089-b33637db3eea. Accessed Mar 2025.

102. Eijsvogel P, Misra P, Concha-Marambio L, Boyd JD, Ding S, Fedor L, et al. Target engagement and immunogenicity of an active immunotherapeutic targeting pathological α-synuclein: a phase 1 placebo-controlled trial. Nat Med. 2024;30(9):2631–40.

103. Turcato F, Kim P, Barnett A, Jin Y, Scerba M, Casey A, et al. Sequential combined treatment of pifithrin-α and posiphen enhances neurogenesis and functional recovery after stroke. Cell Transplant. 2018;27(4):607–21.

104. Teich AF, Sharma E, Barnwell E, Zhang H, Staniszewski A, Utsuki T, et al. Translational inhibition of APP by Posiphen: efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse. A&D Transl Res Clin Interv. 2018;4(1):37–45.

105. Kuo YM, Nwankwo EI, Nussbaum RL, Rogers J, Maccecchini ML. Translational inhibition of α-synuclein by Posiphen normalizes distal colon motility in transgenic Parkinson mice. Am J Neurodegener Dis. 2019;8(1):1–15.

106. Chen X, Salehi A, Pearn ML, Overk C, Nguyen PD, Kleschevnikov AM, et al. Targeting increased levels of APP in Down syndrome: Posiphen-mediated reductions in APP and its products reverse endosomal phenotypes in the Ts65Dn mouse model. Alzheimer's Dementia. 2021;17(2):271–92.

107. Fang C, Hernandez P, Liow K, Damiano E, Zetterberg H, Blennow K, et al. Buntanetap, a novel translational inhibitor of multiple neurotoxic proteins, proves to be safe and promising in both

Alzheimer's and Parkinson's patients. J Prev Alzheimer's Dis. 2023;10(1):25–33.

108. Annovis. Pipeline—Parkinson's studies—Phase 3 Study. Updated 2024. In: https://www.annovisbio.com/pipeline#pipeline. Accessed Mar 2025.

109. Kim S, Choi JG, Kim SW, Park SC, Kang Y, Park DS, et al. Inhibition of α-synuclein aggregation by MT101-5 is neuroprotective in mouse models of Parkinson's disease. Biomed Pharmacother. 2022;154:113637.

110. Price DL, Khan A, Angers R, Cardenas A, Prato MK, Bani M, et al. In vivo effects of the alpha-synuclein misfolding inhibitor minzasolmin supports clinical development in Parkinson's disease. npj Parkinsons Dis. 2023;9(1):114.

111. Volc D, Poewe W, Kutzelnigg A, Lührs P, Thun-Hohenstein C, Schneeberger A, et al. Safety and immunogenicity of the α-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial. Lancet Neurol. 2020;19(7):591–600.

112. Antonschmidt L, Matthes D, Dervişoğlu R, Frieg B, Dienemann C, Leonov A, et al. The clinical drug candidate anle138b binds in a cavity of lipidic α-synuclein fibrils. Nat Commun. 2022;13(1):5385.

113. Levin J, Sing N, Melbourne S, Morgan A, Mariner C, Spillantini MG, et al. Safety, tolerability and pharmacokinetics of the oligomer modulator anle138b with exposure levels sufficient for therapeutic efficacy in a murine Parkinson model: a randomised, double-blind, placebo-controlled phase 1a trial. EBioMedicine. 2022;80:104021.

114. Kim BS, Song JA, Jang KH, Jang T, Jung B, Yoo SE, et al. Pharmacological intervention targeting FAF1 restores autophagic flux for α-synuclein degradation in the brain of a Parkinson's disease mouse model. ACS Chem Neurosci. 2022;13(6):806–17.

115. Shin W, Lim KS, Kim MK, Kim HS, Hong J, Jhee S, et al. A first-in-human study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of KM-819 (FAS-associated factor 1 inhibitor), a drug for Parkinson’s disease, in healthy volunteers. DDDT. 2019;13:1011–22.

116. Schapira AHV. The importance of LRRK2 mutations in Parkinson disease. Arch Neurol. 2006;63(9):1225.

117. Lee C, Menozzi E, Chau K, Schapira AHV. Glucocerebrosidase 1 and leucine-rich repeat kinase 2 in Parkinson disease and interplay between the two genes. J Neurochem. 2021;159(5):826–39.

118. Erb ML, Moore DJ. LRRK2 and the endolysosomal system in Parkinson's disease. JPD. 2020;10(4):1271–91.

119. Senkevich K, Rudakou U, Gan-Or Z. New therapeutic approaches to Parkinson's disease targeting GBA, LRRK2 and Parkin. Neuropharmacology. 2022;202: 108822.

120. Jennings D, Huntwork-Rodriguez S, Henry AG, Sasaki JC, Meisner R, Diaz D, et al. Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease. Sci Transl Med. 2022;14(648):eabj2658.

121. Jennings D, Huntwork-Rodriguez S, Vissers MFJM, Daryani VM, Diaz D, Goo MS, et al. LRRK2 inhibition by BIIB122 in healthy participants and patients with Parkinson's disease. Mov Disord. 2023;38(3):386–98.

122. Menozzi E, Toffoli M, Schapira AHV. Targeting the GBA1 pathway to slow Parkinson disease: insights into clinical aspects, pathogenic mechanisms and new therapeutic avenues. Pharmacol Ther. 2023;246: 108419.

123. Mullin S, Smith L, Lee K, D'Souza G, Woodgate P, Elflein J, et al. Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a nonrandomized, noncontrolled trial. JAMA Neurol. 2020;77(4):427.

124. Colucci F, Avenali M, De Micco R, Fusar Poli M, Cerri S, Stanziano M, et al. Ambroxol as a disease-modifying treatment to reduce the risk of cognitive impairment in GBA-associated Parkinson's disease: a multicentre, randomised, double-blind, placebo-controlled, phase II trial. The AMBITIOUS study protocol. BMJ Neurol Open. 2023;5(2):e000535.

125. Silveira CRA, MacKinley J, Coleman K, Li Z, Finger E, Bartha R, et al. Ambroxol as a novel disease-modifying treatment for Parkinson's disease dementia: protocol for a single-centre, randomized, double-blind, placebo-controlled trial. BMC Neurol. 2019;19(1):20.

126. Giladi N, Alcalay RN, Cutter G, Gasser T, Gurevich T, Höglinger GU, et al. Safety and efficacy of venglustat in GBA1-associated Parkinson's disease: an international, multicentre, double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2023;22(8):661–71.

127. On behalf of the MOVES-PD Investigators, Peterschmitt MJ, Saiki H, Hatano T, Gasser T, Isaacson SH, et al. Safety, pharmacokinetics, and pharmacodynamics of oral venglustat in patients with Parkinson's Disease and a GBA mutation: results from part 1 of the randomized, double-blinded,

placebo-controlled MOVES-PD trial. . JPD. 2022;12(2):557–70.

128. Świątkiewicz M, Zaremba M, Joniec I, Członkowski A, Kurkowska-Jastrzębska I. Potential neuroprotective effect of ibuprofen, insights from the mice model of Parkinson's disease. Pharmacol Rep. 2013;65(5):1227–36.

129. Zaminelli T, Gradowski RW, Bassani TB, Barbiero JK, Santiago RM, Maria-Ferreira D, et al. Antidepressant and antioxidative effect of ibuprofen in the rotenone model of Parkinson's disease. Neurotox Res. 2014;26(4):351–62.

130. Singh A, Tripathi P, Prakash O, Singh MP. Ibuprofen abates cypermethrin-induced expression of pro-inflammatory mediators and mitogen-activated protein kinases and averts the nigrostriatal dopaminergic neurodegeneration. Mol Neurobiol. 2016;53(10):6849–58.

131. Tripathi P, Singh A, Bala L, Patel DK, Singh MP. Ibuprofen protects from cypermethrin-induced changes in the striatal dendritic length and spine density. Mol Neurobiol. 2018;55(3):2333–9.

132. Ramazani E, Tayarani-Najaran Z, Fereidoni M. Celecoxib, indomethacin and ibuprofen prevent 6-hydroxydopamine-induced PC12 cell death through the inhibition of NFκB and SAPK/JNK pathways. Iran J Basic Med Sci [Internet]. 2019. https://doi.org/10.22038/ijbms.2019.34011.8091.

133. Costa T, Fernandez-Villalba E, Izura V, Lucas-Ochoa A, Menezes-Filho N, Santana R, et al. Combined 1-deoxynojirimycin and ibuprofen treatment decreases microglial activation, phagocytosis and dopaminergic degeneration in MPTP-treated mice. J Neuroimmune Pharmacol. 2021;16(2):390–402.

134. Chen H, Jacobs E, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ, et al. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Ann Neurol. 2005;58(6):963–7.

135. Gagne JJ, Power MC. Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis. Neurology. 2010;74(12):995–1002.

136. Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. Neurology. 2011;76(10):863–9.

137. Ren L, Yi J, Yang J, Li P, Cheng X, Mao P. Nonsteroidal anti-inflammatory drugs use and risk of Parkinson disease: a dose–response meta-analysis. Medicine. 2018;97(37): e12172.

138. Chen H, Zhang SM, Hernan MA, Schwarzschild MA, Willett WC, Colditz GA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol. 2003;60(8):1059–64.

139. San Luciano M, Tanner CM, Meng C, Marras C, Goldman SM, Lang AE, et al. Nonsteroidal anti-inflammatory use and LRRK2 Parkinson's disease penetrance. Mov Disord. 2020;35(10):1755–64.

140. Poly TN, Islam MDM, Yang HC, Li YCJ. Non-steroidal anti-inflammatory drugs and risk of Parkinson's disease in the elderly population: a meta-analysis. Eur J Clin Pharmacol. 2019;75(1):99–108.

141. Kuhlman G, Auinger P, Duff-Canning S, Lang A, Tanner C, Marras C. Non-steroidal anti-inflammatory drug use and markers of Parkinson's disease progression: a retrospective cohort study. J Neurol Sci. 2023;454: 120822.

142. Carroll CB, Wyse RKH. Simvastatin as a potential disease-modifying therapy for patients with Parkinson's disease: rationale for clinical trial, and current progress. J Parkinson's Dis. 2017;7(4):545–68.

143. Al-kuraishy HM, Al-Gareeb AI, Alexiou A, Papadakis M, Alsayegh AA, Almohmadi NH, et al. Pros and cons for statins use and risk of Parkinson's disease: an updated perspective. Pharmacol Res Perspect. 2023;11(2): e01063.

144. Lin C, Chang C, Tai C, Cheng M, Chen Y, Chao Y, et al. A double-blind, randomized, controlled trial of lovastatin in early-stage Parkinson's disease. Mov Disord. 2021;36(5):1229–37.

145. Stevens KN, Creanor S, Jeffery A, Whone A, Zajicek J, Foggo A, et al. Evaluation of simvastatin as a disease-modifying treatment for patients with Parkinson disease: a randomized clinical trial. JAMA Neurol. 2022;79(12):1232.

146. Lennard L. The clinical pharmacology of 6-mercaptopurine. Eur J Clin Pharmacol. 1992;43(4):329–39.

147. Tiede I, Fritz G, Strand S, Poppe D, Dvorsky R, Strand D, et al. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. J Clin Investig. 2003;111(8):1133–45.

148. Greenland JC, Cutting E, Kadyan S, Bond S, Chhabra A, Williams-Gray CH. Azathioprine immunosuppression and disease modification in Parkinson's disease (AZA-PD): a randomised double-blind placebo-controlled phase II trial protocol. BMJ Open. 2020;10(11): e040527.

149. Mangano EN, Peters S, Litteljohn D, So R, Bethune C, Bobyn J, et al. Granulocyte macrophage-colony stimulating factor protects against substantia nigra dopaminergic cell loss in an environmental

toxin model of Parkinson's disease. Neurobiol Dis. 2011;43(1):99–112.

150. Kosloski LM, Kosmacek EA, Olson KE, Mosley RL, Gendelman HE. GM-CSF induces neuroprotective and anti-inflammatory responses in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine intoxicated mice. J Neuroimmunol. 2013;265(1–2):1–10.

151. Gendelman HE, Zhang Y, Santamaria P, Olson KE, Schutt CR, Bhatti D, et al. Evaluation of the safety and immunomodulatory effects of sargramostim in a randomized, double-blind phase 1 clinical Parkinson's disease trial. npj Parkinson's Dis. 2017;3(1):10.

152. Olson KE, Abdelmoaty MM, Namminga KL, Lu Y, Obaro H, Santamaria P, et al. An open-label multiyear study of sargramostim-treated Parkinson's disease patients examining drug safety, tolerability, and immune biomarkers from limited case numbers. Transl Neurodegener. 2023;12(1):26.

153. Bachstetter AD, Eldik LJV. The p38 MAP kinase family as regulators of proinflammatory cytokine production in degenerative diseases of the CNS. Aging Dis. 2010;1(3):199–211.

154. Jiang Y, Alam JJ, Gomperts SN, Maruff P, Lemstra AW, Germann UA, et al. Preclinical and randomized clinical evaluation of the p38α kinase inhibitor neflamapimod for basal forebrain cholinergic degeneration. Nat Commun. 2022;13(1):5308.

155. For the REVERSE-SD Study Investigators, Prins ND, Harrison JE, Chu HM, Blackburn K, Alam JJ, et al. A phase 2 double-blind placebo-controlled 24-week treatment clinical study of the p38 alpha kinase inhibitor neflamapimod in mild Alzheimer's disease. Alzheimer's Res Ther. 2021;13(1):106.

156. Wilkins KB, Parker JE, Bronte-Stewart HM. Gait variability is linked to the atrophy of the Nucleus Basalis of Meynert and is resistant to STN DBS in Parkinson's disease. Neurobiol Dis. 2020;146:105134.

157. Wilson J, Yarnall AJ, Craig CE, Galna B, Lord S, Morris R, et al. Cholinergic basal forebrain volumes predict gait decline in Parkinson's disease. Mov Disord. 2021;36(3):611–21.

158. Chen T, Tian P, Huang Z, Zhao X, Wang H, Xia C, et al. Engineered commensal bacteria prevent systemic inflammation-induced memory impairment and amyloidogenesis via producing GLP-1. Appl Microbiol Biotechnol. 2018;102(17):7565–75.

159. Zhang L, Zhang L, Li L, Hölscher C. Semaglutide is neuroprotective and reduces α-synuclein levels in the chronic MPTP mouse model of Parkinson's disease. JPD. 2019;9(1):157–71.

160. Nassar M, Gill AS, Marte E. Investigating the impact of intestinal glucagon-like peptide-1 on hypoglycemia in type 1 diabetes. World J Diabetes [Internet]. 2025;16(3). https://www.wjgnet.com/1948-9358/full/v16/i3/99142.htm. Accessed 11 Apr 2025.

161. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, et al. Exenatide and the treatment of patients with Parkinson's disease. J Clin Investig. 2013;123(6):2730–6.

162. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Kahan J, Ell P, et al. Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. JPD. 2014;4(3):337–44.

163. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10103):1664–75.

164. Athauda D, Gulyani S, Karnati HK, Li Y, Tweedie D, Mustapic M, et al. Utility of neuronal-derived exosomes to examine molecular mechanisms that affect motor function in patients with Parkinson disease: a secondary analysis of the exenatide-PD trial. JAMA Neurol. 2019;76(4):420.

165. Vijiaratnam N, Girges C, Auld G, Chau M, Maclagan K, King A, et al. Exenatide once weekly over 2 years as a potential disease-modifying treatment for Parkinson's disease: protocol for a multicentre, randomised, double blind, parallel group, placebo controlled, phase 3 trial: The 'Exenatide-PD3' study. BMJ Open. 2021;11(5): e047993.

166. Vijiaratnam N, Girges C, Auld G, McComish R, King A, Skene SS, et al. Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial. Lancet. 2025;405(10479):627–36.

167. McGarry A, Rosanbalm S, Leinonen M, Olanow CW, To D, Bell A, et al. Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2024;23(1):37–45.

168. Meissner WG, Remy P, Giordana C, Maltête D, Derkinderen P, Houéto JL, et al. Trial of lixisenatide in early Parkinson's disease. N Engl J Med. 2024;390(13):1176–85.

169. Malatt C, Wu T, Bresee C, Hogg E, Wetheimer J, Tan E, et al. Liraglutide improves non-motor function and activities of daily living in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial (P9-11.005). Neurology. 2022;98(18 Supplement):3068.

170. Meredith GE, Totterdell S, Potashkin JA, Surmeier DJ. Modeling PD pathogenesis in mice: advantages of a chronic MPTP protocol. Parkinsonism Relat Disord. 2008;14:S112–5.

171. Ilijic E, Guzman JN, Surmeier DJ. The L-type channel antagonist isradipine is neuroprotective in a mouse model of Parkinson's disease. Neurobiol Dis. 2011;43(2):364–71.

172. Chen T, Yang Y, Luo P, Liu W, Dai S, Zheng X, et al. Homer1 knockdown protects dopamine neurons through regulating calcium homeostasis in an in vitro model of Parkinson's disease. Cell Signal. 2013;25(12):2863–70.

173. Cooper G, Lasser-Katz E, Simchovitz A, Sharon R, Soreq H, Surmeier DJ, et al. Functional segregation of voltage-activated calcium channels in motoneurons of the dorsal motor nucleus of the vagus. J Neurophysiol. 2015;114(3):1513–20.

174. Wang YL, Wang JG, Guo FL, Gao XH, Zhao DD, Zhang L, et al. Selective dopamine receptor 4 activation mediates the hippocampal neuronal calcium response via IP3 and ryanodine receptors. Brain Res. 2017;1670:1–5.

175. Guzman JN, Ilijic E, Yang B, Sanchez-Padilla J, Wokosin D, Galtieri D, et al. Systemic isradipine treatment diminishes calcium-dependent mitochondrial oxidant stress. J Clin Investig. 2018;128(6):2266–80.

176. Shin J, Kovacheva L, Thomas D, Stojanovic S, Knowlton CJ, Mankel J, et al. Cav1.3 calcium channels are full-range linear amplifiers of firing frequencies in lateral DA SN neurons. Sci Adv. 2022;8(23):eabm4560.

177. Dragicevic E, Schiemann J, Liss B. Dopamine midbrain neurons in health and Parkinson's disease: emerging roles of voltage-gated calcium channels and ATP-sensitive potassium channels. Neuroscience. 2015;284:798–814.

178. Becker C, Jick SS, Meier CR. Use of antihypertensives and the risk of Parkinson disease. Neurology. 2008;70:1438–44.

179. Ritz B, Rhodes SL, Qian L, Schernhammer E, Olsen JH, Friis S. L-type calcium channel blockers and Parkinson disease in Denmark. Ann Neurol. 2010;67(5):600–6.

180. Cepeda MS, Kern DM, Seabrook GR, Lovestone S. Comprehensive real-world assessment of marketed medications to guide Parkinson's drug discovery. Clin Drug Investig. 2019;39(11):1067–75.

181. Uchida S, Yamada S, Nagai K, et al. Brain pharmacokinetics and in vivo receptor binding of 1,4-dihydropyridine calcium channel antagonists. Life Sci. 1997;61:2083–90.

182. McDonagh MS, Eden KB, Peterson K. Drug class review: calcium channel blockers: final report [Internet]. Portland: Oregon Health and Science University; 2005.

183. The Parkinson Study Group STEADY-PD III Investigators. Isradipine versus placebo in early Parkinson disease: a randomized trial. Ann Intern Med. 2020;172(9):591–8.

184. Surmeier DJ, Nguyen JT, Lancki N, Venuto CS, Oakes D, Simuni T, et al. Re-analysis of the STEADY-PD II trial—evidence for slowing the progression of Parkinson's disease. Mov Disord. 2022;37(2):334–42.

185. Murata M, Hasegawa K, Kanazawa I, The Japan Zonisamide on PD Study Group. Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study. Neurology. 2007;68(1):45–50.

186. Murata M, Hasegawa K, Kanazawa I, Fukasaka J, Kochi K, Shimazu R, et al. Zonisamide improves wearing-off in Parkinson's disease: a randomized, double-blind study. Mov Disord. 2015;30(10):1343–50.

187. Murata M, Odawara T, Hasegawa K, Kajiwara R, Takeuchi H, Tagawa M, et al. Effect of zonisamide on parkinsonism in patients with dementia with Lewy bodies: a phase 3 randomized clinical trial. Parkinsonism Relat Disord. 2020;76:91–7.

188. Asanuma M, Miyazaki I, Diaz-Corrales FJ, Kimoto N, Kikkawa Y, Takeshima M, et al. Neuroprotective effects of zonisamide target astrocyte. Ann Neurol. 2010;67(2):239–49.

189. Sonsalla PK, Wong LY, Winnik B, Buckley B. The antiepileptic drug zonisamide inhibits MAO-B and attenuates MPTP toxicity in mice: clinical relevance. Exp Neurol. 2010;221(2):329–34.

190. Yürekli VA, Gürler S, Nazıroğlu M, Uğuz AC, Koyuncuoğlu HR. Zonisamide attenuates MPP(+)-induced oxidative toxicity through modulation of Ca2+ signaling and caspase-3 activity in neuronal PC12 cells. Cell Mol Neurobiol. 2013;33(2):205–12.

191. Yang YC, Tai CH, Pan MK, Kuo CC. The T-type calcium channel as a new therapeutic target for Parkinson's disease. Pflugers Arch Eur J Physiol. 2014;466(4):747–55.

192. Tsujii S, Ishisaka M, Shimazawa M, Hashizume T, Hara H. Zonisamide suppresses endoplasmic reticulum stress-induced neuronal cell damage in vitro and in vivo. Eur J Pharmacol. 2015;746:301–7.

193. Hossain MM, Weig B, Reuhl K, Gearing M, Wu LJ, Richardson JR. The anti-parkinsonian drug zonisamide reduces neuroinflammation: role of microglial Nav 1.6. Exp Neurol. 2018;308:111–9.

194. Ikeda K, Yanagihashi M, Miura K, Ishikawa Y, Hirayama T, Takazawa T, et al. Zonisamide cotreatment delays striatal dopamine transporter reduction in Parkinson disease: a retrospective, observational cohort study. J Neurol Sci. 2018;391:5–9.

195. Iwaki H, Tagawa M, Iwasaki K, Kawakami K, Nomoto M. Comparison of zonisamide with nonlevodopa, anti-Parkinson's disease drugs in the incidence of Parkinson's disease-relevant symptoms. J Neurol Sci. 2019;402:145–52.

196. Terada T, Bunai T, Hashizume T, Matsudaira T, Yokokura M, Takashima H, et al. Neuroinflammation following anti-parkinsonian drugs in early Parkinson's disease: a longitudinal PET study. Sci Rep. 2024;14(1):4708.

197. Blandini F. Neuroprotection by rasagiline: a new therapeutic approach to Parkinson's disease? CNS Drug Rev. 2005;11(2):183–94.

198. Youdim M. The path from anti Parkinson drug selegiline and rasagiline to multifunctional neuroprotective anti Alzheimer drugs ladostigil and M30. CAR. 2006;3(5):541–50.

199. Mandel SA, Sagi Y, Amit T. Rasagiline promotes regeneration of substantia nigra dopaminergic neurons in post-MPTP-induced Parkinsonism via activation of tyrosine kinase receptor signaling pathway. Neurochem Res. 2007;32(10):1694–9.

200. Weinreb O, Amit T, Sagi Y, Drigues N, Youdim MBH. Genomic and proteomic study to survey the mechanism of action of the anti-Parkinson's disease drug, rasagiline compared with selegiline, in the rat midbrain. J Neural Transm. 2009;116(11):1457–72.

201. Weinreb O, Amit T, Bar-Am O, Youdim MBH. Rasagiline: a novel anti-Parkinsonian monoamine oxidase-B inhibitor with neuroprotective activity. Prog Neurobiol. 2010;92(3):330–44.

202. Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med. 2009;361(13):1268–78.

203. Rascol O, Hauser RA, Stocchi F, Fitzer-Attas CJ, Sidi Y, Abler V, et al. Long-term effects of rasagiline and the natural history of treated Parkinson's disease. Mov Disord. 2016;31(10):1489–96.

204. Magistrelli L, Comi C. Beta2-adrenoceptor agonists in Parkinson's disease and other synucleinopathies. J Neuroimmune Pharmacol. 2020;15(1):74–81.

205. Joint Formulary Committee. Salbutamol. In: Joint Formulary Committee. British National Formulary [BNF online][]. London: BMJ Group and Pharmaceutical Press; 2025. https://bnf.nice.org.uk/drugs/salbutamol/. Accessed Jan 2025.

206. Mittal S, Bjørnevik K, Im DS, Flierl A, Dong X, Locascio JJ, et al. β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. Science. 2017;357(6354):891–8.

207. Searles Nielsen S, Gross A, Camacho-Soto A, Willis AW, Racette BA. β2-Adrenoreceptor medications and risk of Parkinson disease. Ann Neurol. 2018;84(5):683–93.

208. Hishida R, Kurahashi K, Shoko N, Baba T, Muneo M. 'Wearing-off' and beta 2-adrenoceptor agonist in Parkinson's disease. Lancet. 1992;339(8797):870.

209. Alexander GM, Schwartzman RJ, Nukes TA, Grothusen JR, Hooker MD. β2-Adrenergic agonist as adjunct therapy to levodopa in Parkinson's disease. Neurology. 1994;44(8):1511–1511.

210. Uc EY, Lambert CP, Harik SI, Rodnitzky RL, Evans WJ. Albuterol improves response to levodopa and increases skeletal muscle mass in patients with fluctuating Parkinson disease. Clin Neuropharmacol. 2003;26(4):207–12.

211. Australian New Zealand Clinical Trials Registry. https://www.64anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375958&65isReview=true. Accessed 13 Apr 2025.

212. The FAIRPARK-II and FAIRALS-II Studygroups, Devos D, Cabantchik ZI, Moreau C, Danel V, Mahoney-Sanchez L, et al. Conservative iron chelation for neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis. J Neural Transm. 2020;127(2):189–203.

213. Joint Formulary Committee. Deferiprone. In: Joint Formulary Committee. British National Formulary [BNF online]. London: BMJ Group and Pharmaceutical Press; 2025. https://bnf.nice.org.uk/drugs/deferiprone/. Accessed Jan 2025.

214. Devos D, Moreau C, Devedjian JC, Kluza J, Petrault M, Laloux C, et al. Targeting chelatable iron as a therapeutic modality in Parkinson's disease. Antioxid Redox Signal. 2014;21(2):195–210.

215. Martin-Bastida A, Ward RJ, Newbould R, Piccini P, Sharp D, Kabba C, et al. Brain iron chelation by deferiprone in a phase 2 randomised double-blinded placebo controlled clinical trial in Parkinson's disease. Sci Rep. 2017;7(1):1398.

216. Devos D, Labreuche J, Rascol O, Corvol JC, Duhamel A, Guyon Delannoy P, et al. Trial of

deferiprone in Parkinson's disease. N Engl J Med. 2022;387(22):2045–55.

217. Rafferty MR, Schmidt PN, Luo ST, Li K, Marras C, Davis TL, et al. Regular exercise, quality of life, and mobility in Parkinson's disease: a longitudinal analysis of National Parkinson Foundation Quality Improvement Initiative Data. J Parkinson's Dis. 2016;7(1):193–202.

218. Rafferty MR, Prodoehl J, Robichaud JA, David FJ, Poon C, Goelz LC, et al. Effects of 2 years of exercise on gait impairment in people with Parkinson disease: the PRET-PD randomized trial. J Neurol Phys Ther. 2017;41(1):21–30.

219. Tsukita K, Sakamaki-Tsukita H, Takahashi R. Long-term effect of regular physical activity and exercise habits in patients with early Parkinson disease. Neurology [Internet]. 2022. https://doi.org/10.1212/WNL.0000000000013218.

220. Yoon SY, Suh JH, Yang SN, Han K, Kim YW. Association of physical activity, including amount and maintenance, with all-cause mortality in Parkinson disease. JAMA Neurol. 2021;78(12):1446.

221. Mak MK, Wong-Yu IS, Shen X, Chung CL. Long-term effects of exercise and physical therapy in people with Parkinson disease. Nat Rev Neurol. 2017;13(11):689–703.

222. Van Der Kolk NM, De Vries NM, Kessels RPC, Joosten H, Zwinderman AH, Post B, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. Lancet Neurol. 2019;18(11):998–1008.

223. Schootemeijer S, De Vries NM, Macklin EA, Roes KCB, Joosten H, Omberg L, et al. The STEPWISE study: study protocol for a smartphone-based exercise solution for people with Parkinson's disease (randomized controlled trial). BMC Neurol. 2023;23(1):323.

224. Schootemeijer S, De Vries NM, Darweesh SKL, Ascherio A, Schwarzschild MA, Macklin EA, et al. Promoting physical activity in people with Parkinson's disease through a smartphone app: a pilot study. J Neurol Phys Ther. 2025;49(2):74–81.

225. Schootemeijer S, Darweesh SKL, De Vries NM. Clinical trial highlights—aerobic exercise for Parkinson's disease. JPD. 2022;12(8):2297–306.