hhttps://doi.org/10.14802/jmd.25008 / J Mov Disord 2025;18(2):113-126
pISSN 2005-940X / eISSN 2093-4939

REVIEW ARTICLE

Drug Repositioning and Repurposing for Disease-Modifying Effects in Parkinson's Disease

Seong Ho Jeong,[1] Phil Hyu Lee[2,3] ✉

[1]Department of Neurology, Inje University Sanggye Paik Hospital, Seoul, Korea
[2]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[3]Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder and is characterized by progressive dopaminergic and nondopaminergic neuronal loss and the presence of Lewy bodies, which are primarily composed of aggregated α-synuclein. Despite advancements in symptomatic therapies, such as dopamine replacement and deep brain stimulation, no disease-modifying therapies (DMTs) have been identified to slow or arrest neurodegeneration in patients with PD. Challenges in DMT development include disease heterogeneity, the absence of reliable biomarkers, and the multifaceted pathophysiology of PD, encompassing neuroinflammation, mitochondrial dysfunction, lysosomal impairment, and oxidative stress. Drug repositioning and repurposing strategies using existing drugs for new therapeutic applications offer promising approaches to accelerate the development of DMTs for PD. These strategies minimize time, cost, and risk by using compounds with established safety profiles. Prominent candidates include glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, ambroxol, calcium channel blockers, statins, iron-chelating agents, c-Abl inhibitors, and memantine. Although preclinical and early clinical studies have demonstrated encouraging results, numerous phase III trials have yielded unfavorable outcomes, elucidating the complexity of PD pathophysiology and the need for innovative trial designs. This review evaluates the potential of prioritized repurposed drugs for PD, focusing on their mechanisms, preclinical evidence, and clinical trial outcomes, and highlights the ongoing challenges and opportunities in this field.

Keywords Parkinson's disease; Synucleinopathy; Drug repurposing; Drug repositioning; Glucagon-like peptide-1 agonist; Dipeptidyl peptidase-4 inhibitor.

Parkinson's disease (PD) is characterized by progressive dopaminergic and nondopaminergic neuronal degeneration, which contributes to motor and nonmotor symptoms, and affects millions of individuals worldwide.[1] Despite significant advancements in symptomatic treatments, these interventions fail to modify the course of neurodegeneration, highlighting the urgent need for disease-modifying therapies (DMTs) that can slow or arrest disease progression.[2]

Lewy bodies, resulting from α-synuclein aggregation, are the core pathological feature of PD.[1] Neuroinflammation, proteasome and lysosome dysfunction, and mitochondrial dysfunction and α-synuclein propagation (i.e., cell-to-cell transmission of α-synuclein) are significant factors in the pathophysiology of PD (Figure 1).[3,4] A recent review of the clinical registry identified only 38 ongoing phase II or phase III pharmacological or biological treatments for disease modification in PD.[5] Moreover, the number of randomized clinical trials of DMTs for PD has not increased since 2020. Despite the substantial potential value of effective DMTs for PD, this area of research is considered high risk by the pharmaceutical industry, particularly be-

Received: January 15, 2025 **Revised:** February 4, 2025 **Accepted:** February 7, 2025
✉ **Corresponding author:** Phil Hyu Lee, MD, PhD
Department of Neurology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea / **Tel:** +82-2-2228-1608 / **Fax:** +82-2-393-0705 / **E-mail:** phlee@yuhs.ac

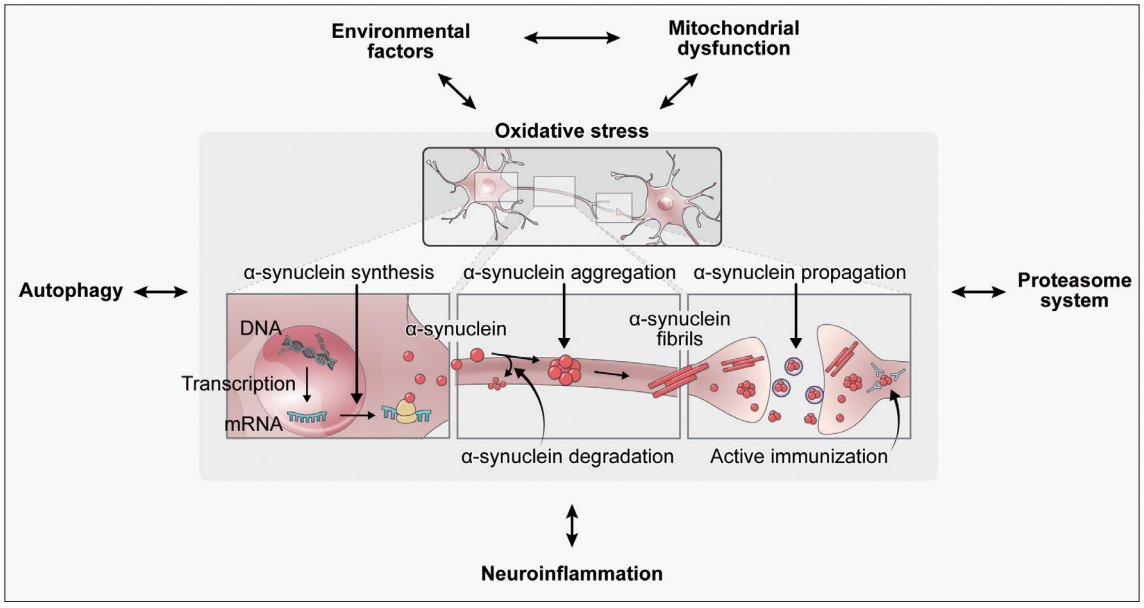

Figure 1. Pathophysiological mechanisms of α-synuclein in Parkinson's disease. This figure illustrates the interplay between environmental factors, mitochondrial dysfunction, and oxidative stress in promoting the pathological expression of α-synuclein, a key protein implicated in Parkinson's disease.

cause of the low clinical trial success rate. Notably, the challenges that contribute to repeated failures in phase III trials are complex and multifactorial. Disease heterogeneity, lack of reliable biomarkers for early diagnosis and disease progression, and limitations in trial design may limit the success of DMTs in the PD field.[6,7] Additionally, the neurodegenerative processes underlying PD are multifaceted and involve not only dopaminergic neuron loss but also multiple pathomechanisms. This complicates the identification of single agents capable of modifying disease progression.[3,8]

DRUG REPOSITIONING AND REPURPOSING

Drug repositioning in the biopharmaceutical industry refers to the process of developing a drug for a new indication that differs from its original purpose, with the new indication taking precedence during the development phase prior to approval. In contrast, drug repurposing involves applying existing drug compounds to address new therapeutic conditions; specifically, it is a pathway accessible to academic institutions, government and research councils, charities, and nonprofit organizations, complementing the efforts of pharmaceutical and biotech companies.[9] Both repositioning and repurposing provide promising strategies to enhance traditional drug development and expedite the introduction of new treatments for PD in clinical practice. When conducting phase II trials for repurposed drugs, it is crucial to identify the optimal target population for the therapy and align it with the mechanism of action of the treatment. A notable example of this in PD is amantadine, which provides symptomatic relief of motor symptoms or exerts an antidyskinetic effect.[10]

A significant advantage of this approach is that the safety profile of the candidate compound has already been established, eliminating the need for further preclinical safety testing, chemical optimization, or toxicology studies. Notably, this substantially reduces both the time and cost required to advance potential treatments in clinical trials. Furthermore, drugs already on the market typically have extensive safety data from prior regulatory programs, postmarketing surveillance, and safety monitoring. This well-documented safety profile often provides a strong foundation, or "freedom to operate," particularly when existing drugs are repurposed for vulnerable populations, such as individuals with PD. Additionally, drug repurposing may bypass early developmental stages, including preclinical testing and phase II and phase IIa trials, which are time intensive and associated with high rates of drug attrition. Many hidden costs in drug development, such as formulation optimization, manufacturing processes, and drug-drug interaction studies, are also often addressed by the original developer. Although the average cost of bringing a drug to market is estimated at $5.6 billion, programs focused on repurposed drugs can significantly lower these expenses.[11] Furthermore, for repurposed agents, clinical evidence of efficacy may already exist through pathophysiological insights, epidemiological studies, open-label trials, or preliminary clinical

data, providing a valuable supplement to the evidence base, particularly given the limitations of animal models.

Various strategies can be used to identify potential drug candidates for repurposing. One approach involves analyzing large datasets to uncover drug-related patient outcomes that might otherwise go unnoticed.[12,13] Another method, namely, hypothesis-driven repurposing, integrates knowledge of the disease and the properties or targets of existing drugs to pinpoint promising candidates.[14] Moreover, high-throughput screening using in vitro models to evaluate the effects of compounds on mechanisms such as α-synuclein aggregation is another useful technique.[15] A newer approach leverages disease-associated transcriptional signatures to identify potential therapies.[16] Combining these methods with a manual review of the literature is yet another strategy for identifying repurposing candidates. However, the available evidence varies among compounds; some may have robust in vitro or in vivo data, whereas others may rely on strong epidemiological findings. Notably, any proposed treatment, such as that for older adults with PD, should be appropriate for the target population. Addressing this complexity can be achieved by systematically reviewing the evidence and incorporating expert consensus methodologies such as the International Linked Clinical Trials Initiative (iLCT).[17] This standardized method combines evidence review with iterative expert re-evaluation to establish priorities and select viable candidates.

We aim to discuss the drugs among the prioritized candidate drugs designated by the iLCT committee that have undergone or are currently undergoing clinical trials, as well as memantine, which has been investigated in our own research. Clinical trials of repurposed drugs for PD are presented in Table 1. Additionally, Figure 2 illustrates the mechanisms by which each drug discussed in this review is expected to exert a promising disease-modifying effect on α-synuclein, the central pathological hallmark of PD. The drug repositioning evidence levels for each drug,[18] ranging from 0 (prediction only) to 4 (well-documented clinical endpoints), are illustrated in Figure 3.

PRIORITIZED DRUGS IN PREVIOUS RESEARCH

Glucagon-like peptide-1 receptor agonists

Owing to their potential neuroprotective properties in PD, glucagon-like peptide-1 (GLP-1) receptor agonists represent a category of antidiabetic medications that have garnered interest. The main actions of GLP-1 are to control glucose levels by stimulating insulin secretion and inhibiting glucagon secretion. However, GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4), leading to the formation of inactive metabolites. Consequently, GLP-1 receptor agonists, such as exenatide, lixisenatide, and liraglutide, which are resistant to DPP-4 degradation, are frequently utilized in the management of type 2 diabetes mellitus.[19,20] Both GLP-1 and its receptor are expressed in neuronal tissues, and their activation has been associated with beneficial outcomes in terms of cell proliferation, neurogenesis, and apoptosis.[21] Additionally, insulin resistance has attracted attention as a potential contributor to neurodegenerative processes.[22] Specifically, research indicates that GLP-1 receptor agonists may be associated with a reduced risk of developing PD among individuals with diabetes,[13] and these agents have demonstrated neuroprotective effects in various models of neurotoxicity and α-synucleinopathy related to PD.[23-25] A proof-of-concept, single-blind study involving 21 patients with moderate PD who received exenatide for 12 months revealed sustained improvements in motor and cognitive functions for up to 14 months posttreatment, even after a 2-month wash-out period.[26] Furthermore, a phase IIb clinical trial successfully met its primary endpoint, showing a significant reduction in the progression of motor symptoms, as assessed by the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, following 48 weeks of double-blind treatment.[27] Similarly, the potential of another GLP-1 receptor agonist, lixisenatide, in the treatment of PD has attracted considerable attention due to promising findings.[28] Compared with those receiving placebo, participants receiving lixisenatide exhibited decreased disability, as measured by the MDS-UPDRS part III, with these improvements observed in both the on- and off-medication states. This finding suggests that lixisenatide has disease-modifying effects that extend beyond enhancing the efficacy of existing therapeutic interventions.

In contrast, NLY-01, which is a longer-lasting version of exenatide, failed to show effectiveness on disease progression in patients with PD after 36 weeks of treatment.[29] Unlike other studies, the NLY-01 study was conducted in patients with drug-naïve PD, and its negative results suggest that the effects of GLP-1 receptor agonists observed in other clinical trials may be more likely to represent a symptomatic effect by enhancing the efficacy of levodopa rather than a true disease-modifying effect. Similarly, although some nonmotor symptoms improved, administration of liraglutide did not result in a difference in the MDS-UPDRS part III score between the treatment and control groups.[30]

Nevertheless, GLP-1 receptor agonists are anticipated to have potential disease-modifying effects on PD. However, a recent phase III clinical trial of exenatide (exenatide-PD3) indicated a lack of efficacy. Although the final results have not yet been published, they are expected to provide valuable insights for future clinical trials of other drugs, including lixisenatide.

Table 1. Clinical trials of repurposed drugs for investigating disease modifying effects on Parkinson's disease

Mechanism of action	Agent	Phase	Number	Study population	Dose	Duration	Primary outcome	Results
GLP-1 receptor agonists	Exenatide[26]	Pilot study	45	Moderate PD	2 mg sc once weekly vs. placebo	60 weeks (8 weeks wash-out period)	ΔMDS-UPDRS III (OFF state) at each month	Positive; ΔMDS-UPDRS III -2.7 (exenatide) vs. 2.2 (placebo) (p=0.037)
	Exenatide[27]	Phase II	60	Moderate PD	2 mg sc once weekly vs. placebo	60 weeks (12 weeks wash-out period)	ΔMDS-UPDRS III (OFF state) at week 60	Positive; ΔMDS-UPDRS III -1.0 (exenatide) vs. 2.1 (placebo) (p=0.0318)
	Exenatide	Phase III (not published yet)	194	Moderate PD	2 mg sc once weekly vs. placebo	96 weeks	ΔMDS-UPDRS I–III (OFF state) at week 96	Negative
	Lixisenatide[28]	Phase IIb	62	Early PD (Dx <3 yrs)	10 μg/day×14 days, then 20 μg/day vs. placebo	60 weeks (8 weeks wash-out period)	ΔMDS-UPDRS III (ON state) at month 12	Positive; ΔMDS-UPDRS III -0.04 (lixisenatide) vs. 3.04 (placebo) (p=0.007)
	Liraglutide[30]	Phase II	63	Moderate PD	1.2 mg or 1.8 mg sc daily vs. placebo	54 weeks (2 weeks wash-out period)	ΔMDS-UPDRS III (OFF state) at week 54	Negative
	NLY-01[29]	Phase II	255	Drug-naïve PD	2.5 mg vs. 5.0 mg vs. placebo (1:1:1 ratio)	36 weeks	ΔMDS-UPDRS II and III (OFF state) at week 36	Negative
DPP-4 inhibitors	Alogliptin	Phase II	240	Moderate PD	Alogliptin 25 mg/day vs. albuterol SR vs. nilvadipine vs. placebo (four arms)	60 weeks (12 weeks wash-out period)	ΔMDS-UPDRS III (OFF state) at week 60	Ongoing; not completed
	Sitagliptin	Phase IV	12	PD or LBD	Sitagliptin 100 mg/day vs. dapagliflozin 10 mg/day vs. placebo	4 weeks	ΔMDS-UPDRS III and ΔMMSE at week 4	Ongoing; not completed
GBA	Ambroxol[52]	Phase IIa	18	Moderate PD	Escalating dose to 1,260 mg daily	186 days	GCase, ambroxol levels in blood, CSF	Positive; decrease in GCase activity by 19% (p=0.04), increased CSF ambroxol
	Ambroxol (AMBITIOUS)	Phase II	60	GBA-PD	1.2 g/day vs. placebo	52 weeks	ΔMoCA at week 4; conversion rate to MCI or dementia	Ongoing; not completed
	Ambroxol	Phase II	55	Mild to moderate PDD	1,050 mg/day vs. 525 mg/day vs. placebo	52 weeks	ΔADAS-cog, ADCS-CGIC at weeks 26 and 52	Ongoing; not completed
	Ambroxol (ANeED)	Phase IIa	172	DLB	Escalating dose to 1,260 mg/day vs. placebo	78 weeks	ΔMMSE at week 78	Ongoing; not completed
	Ambroxol (ASPro-PD)	Phase III	330	PD with confirmed GBA status	1,260 mg/day vs. placebo	104 weeks	ΔMDS-UPDRS I–III (OFF state) at week 104	Ongoing; not completed
Calcium channel blockers	Isradipine[60]	Phase III	336	Early PD (Dx <3 yrs)	5 mg twice daily vs. placebo	36 months	ΔUPDRS I–III at month 36	Negative

Table 1. Clinical trials of repurposed drugs for investigating disease modifying effects on Parkinson's disease (cotinued)

Mechanism of action	Agent	Phase	Number	Study population	Dose	Duration	Primary outcome	Results
Statins	Simvastatin[73]	Phase II	235	Moderate PD	80 mg/day vs. placebo	26 months (2 months washout period)	ΔMDS-UPDRS I–III (OFF state) at month 24	Negative (worsened motor outcomes; ΔMDS-UPDRS III -4.5 (simvastatin) vs. 2.4 (placebo) (p=0.003)
	Lovastatin[74]	Phase II	77	Early PD (H&Y stage <3)	80 mg/day vs. placebo	52 weeks (4 weeks wash-out period)	ΔMDS-UPDRS I–III (OFF state) at week 48	Negative
Iron chelators	Deferiprone (FAIRPARK)[80]	Phase II	372	Early PD (disease duration <18 months)	15 mg/kg twice daily vs. placebo	36 weeks	ΔMDS-UPDRS I–III (OFF state) at week 36	Reduced iron but worsened motor scores
	Deferiprone (SKY and EMBARK)[81]	Phase II	176*	Early PD (Dx <3 yrs)	Randomized 1:1 to one of four dosage (or placebo-matching) cohorts (300, 600, 900, 1,200 mg twice daily) (SKY); 15 mg/kg (EMBARK)	9 months	ΔMDS-UPDRS III at month 9	Negative (deferiprone combined with L-dopa does not provide significant motor function benefit, while the absence of L-dopa treatment worsens symptoms)
c-Abl inhibitors	Nilotinib (NILO-PD)[88]	Phase II	76	Moderate PD	150 mg or 300 mg once daily vs. placebo	6 months	Safety and tolerability	Safe and well-tolerated (no changes in DA metabolites)
	Nilotinib[87]	Phase II	75	Moderate PD	150 mg or 300 mg once daily vs. placebo	12 months	Safety and tolerability	Reasonably safe, increased CSF levels of DA metabolites
	K0706 (Vodobatinib)	Phase II (not published)	513	Early PD (Dx <3 yrs)	Low dose vs. high dose once daily vs. placebo	40 weeks	ΔMDS-UPDRS II–III at week 40	No evidence of benefit
NMDAR antagonist	Memantine	Phase III	50	Moderate PD	20 mg/day vs. placebo	51 weeks	ΔScores of cognitive test items at week 40	Ongoing; not completed
ROCK inhibitors	Fasudil	Phase IIa	75	Early PD	44 mg/day vs. 22 mg/day vs. placebo	50 days	Safety and tolerability	Ongoing; not completed
Glycolysis enhancers	Terazosin[103]	Pilot study	13	PD	5 mg/day vs. placebo	12 weeks	ATP levels	Increased ATP levels
SGLT-2 inhibitors	Dapagliflozin	Phase IV	12	PD or LBD	Sitagliptin 100 mg/day vs. dapagliflozin 10 mg/day vs. placebo	4 weeks	ΔMDS-UPDRS III and ΔMMSE at week 4	Ongoing; not completed

*140 participants in the SKY study and 36 participants in the EMBARK study.
GLP-1, glucagon-like peptide-1; PD, Parkinson's disease; sc, subcutaneous; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; Dx, diagnosis; DPP-4, dipeptidyl peptidase-4; SR, sustained-release; LBD, Lewy body dementia; MMSE, Mini-Mental State Examination; GBA, glucocerebrosidase; GCase, β-glucocerebrosidase; CSF, cerebrospinal fluid; MoCA, Montreal Cognitive Assessment; MCI, mild cognitive impairment; PDD, Parkinson's disease dementia; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-CGIC, Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change; DLB, dementia with Lewy bodies; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y stage, Hoehn and Yahr stage; c-Abl, Abelson murine leukemia viral homolog 1; DA, dopamine; NMDAR, N-methyl-D-aspartate recptor; ROCK, Rho-associated protein kinase; APT, adenosine triphosphate; SGLT-2, sodium-glucose cotransporter-2.

J Mov Disord 2025;18(2):113-126

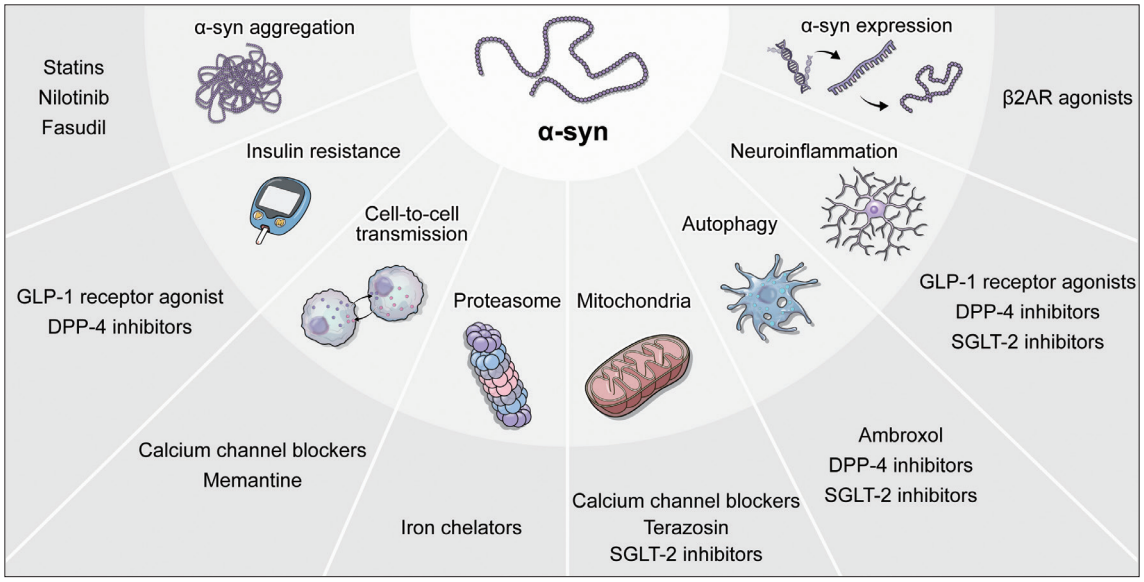

Figure 2. Proposed mechanisms of drug repurposing of α-synuclein in Parkinson's disease. This figure illustrates various repurposed drugs and their mechanisms of action targeting the core protein α-synuclein in Parkinson's disease. The surrounding layers represent drug categories and their respective mechanisms of action. α-syn, α-synuclein; β2AR, β2-adrenergic receptor; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose cotransporter-2.

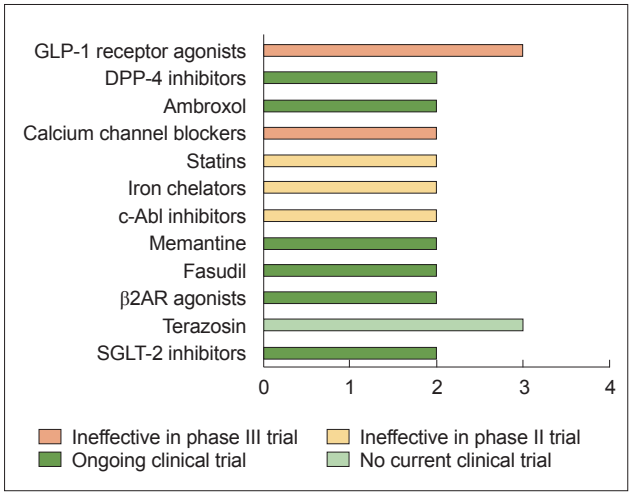

Figure 3. Drug repositioning evidence levels in Parkinson's disease. The figure categorizes various drug classes based on their level of clinical evidence for repurposing in Parkinson's disease. The evidence levels are defined as follows: level 0, no evidence; includes in silico predictions without experimental validation; level 1, in vitro studies with limited value for predicting in vivo or human outcomes; level 2, animal studies with hypothetical relevance to human disease; level 3, incomplete studies in humans at appropriate doses, such as proof-of-concept trials or observational studies with limited clinical data; and level 4, well-documented clinical endpoints observed for the repurposed drug at doses within established safety limits. The evidence levels are depicted in the bars, with categories including "Ineffective in phase III trials" (orange), "Ineffective in phase II trials" (light yellow), "Ongoing clinical trials" (dark green), and "No current clinical trials" (light green). GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; c-Abl, Abelson murine leukemia viral homolog 1; β2AR, β2-adrenergic receptor; SGLT-2, sodium-glucose cotransporter-2.

DPP-4 inhibitors

Preclinical research has indicated that DPP-4 inhibitors may protect dopaminergic neurons from degeneration, promote neuroplasticity, and reduce neuroinflammation.[31-35] Although their primary mechanism involves enhancing GLP-1 signaling and its associated anti-inflammatory effects,[36] direct inhibition of DPP-4 may provide additional anti-inflammatory benefits.[37] This dual mechanism suggests that DPP-4 inhibitors can have comprehensive neuroprotective effects in patients with PD. In addition, given that DPP-4 inhibitors are small molecules, they offer practical advantages over larger peptide-based therapies such as GLP-1 receptor agonists, making them more suitable for patients with PD.[38]

A nationwide case-control study conducted in Sweden indicated that the administration of DPP-4 inhibitors is linked to a reduced risk of developing PD in the future.[39] Similarly, another cohort study revealed that the utilization of DPP-4 inhibitors and/or GLP-1 receptor agonists was associated with a lower incidence of PD than other oral antidiabetic medications.[13] Furthermore, research by Lin et al.[40] revealed that diabetic patients receiving DPP-4 inhibitors, particularly vildagliptin, presented a significantly lower risk of PD than did those treated with alternative oral antidiabetic drugs. Additionally, a recent investigation highlighted that diabetic patients with PD treated with DPP-4 inhibitors demonstrated greater baseline dopamine transporter availability and a slower escalation in levodopa-equivalent dosage over time, indicating potential beneficial effects on motor outcomes within this population.[41]

A multiarm phase II trial conducted in Australia recruited 240 participants who were randomly assigned to one of four arms: a placebo arm against an albuterol arm, a nilvadipine arm, and an alogliptin arm, which is a DPP-4 inhibitor (registration number: ACTRN12620000560998). Additionally, a small phase IV study investigated the beneficial effects of sitagliptin, a DPP-4 inhibitor, and dapagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, on Lewy body disease (ID: NCT06263673). Although the recent phase III trial of exenatide yielded negative results, raising doubts about the effectiveness of DPP-4 inhibitors for treating PD, DPP-4 has various nonglycemic effects beyond its mechanism of inhibiting GLP-1 degradation.[42] Notably, DPP-4 inhibitors play a critical role in modulating inflammatory responses, which suggests potential therapeutic effects in PD.[37] For example, DPP-4 influences signaling pathways related to inflammatory cytokines, indicating the possibility of suppressing microglial activation and neuroinflammation in the brain. Additionally, DPP-4 inhibitors may affect cellular processes such as apoptosis, which could play a significant role in neurodegenerative diseases such as PD.[43] Therefore, drawing definitive conclusions about the potential disease-modifying effects of DPP-4 inhibitors in PD remains challenging. Further studies are needed to evaluate these effects, particularly through experimental approaches that focus on nonglycemic effects. Such research could provide more specific and in-depth insights into this area.

Ambroxol

In 2009, ambroxol hydrochloride, a commonly used expectorant for the management of respiratory conditions characterized by excessive mucus production, was identified as a chaperone for the lysosomal enzyme β-glucocerebrosidase (GCase), which is encoded by the *GBA1* gene, during a screening of drugs approved by the Food and Drug Administration.[44] This finding indicates the potential for repurposing ambroxol for the treatment of PD, given that genetic mutations in the *GBA1* gene are the strongest genetic risk factor for PD.[45] Under normal circumstances, GCase operates as a lysosomal enzyme; however, mutations in *GBA1* result in the enzyme being sequestered within the endoplasmic reticulum (ER), leading to its degradation by the proteasome.[46] This mechanism is believed to contribute to the lysosomal dysfunction observed in both Gaucher disease and PD. Patients with PD with *GBA1* mutations exhibit symptoms similar to those of patients with idiopathic PD, albeit with a more aggressive clinical course characterized by a younger onset of symptoms, rapid motor progression, and rapid cognitive decline.[47] Furthermore, subsequent to the identification of ambroxol's function as a GCase chaperone, research has demonstrated its capacity to increase GCase levels within the central nervous system in various in vitro and in vivo models.[48-50] Ambroxol translocates mutant GCase from the ER to lysosomes, thereby increasing cellular GCase activity.[51] Additionally, ambroxol has been shown to decrease the levels of α-synuclein and its phosphorylated variant in the brains of mice that overexpress human α-synuclein.[49]

Motivated by these preclinical findings, the phase IIa "AiM-PD" trial started and enrolled 18 patients with PD who were administered escalating doses of ambroxol (up to 1,260 mg/day) over 6 months. Recent results indicated that ambroxol was tolerable for patients with PD and that adverse events were not significant. Additionally, ambroxol significantly increased GCase levels in the cerebrospinal fluid (CSF) by approximately 35%.[52] However, due to the open-label design and limited duration of the study, these results require cautious interpretation. Two clinical trials are currently underway to expand these findings. Specifically, the AMBITIOUS trial, a phase II study, examined the impact of ambroxol on cognitive decline in PD patients with *GBA1* mutations. This double-blind, placebo-controlled trial evaluated primary cognitive outcomes and secondary measures, including motor and nonmotor symptoms and biomarkers of neurodegeneration. Additionally, the ASPro-PD trial, a phase III study, aimed to assess the safety, tolerability, and potential disease-modifying effects of ambroxol in a broader population of patients with PD. These trials represent essential advancements in efforts to translate preclinical success into clinically significant outcomes. Additionally, another phase II study investigated ambroxol in 70 PD patients with dementia.[53] In Norway, the ANeED study is recruiting participants, focusing on dementia with Lewy bodies (DLB) in a phase IIa multicenter trial.[54] These ongoing clinical trials reflect growing optimism about the therapeutic potential of ambroxol for PD, as researchers aim to translate promising preclinical findings into meaningful clinical outcomes for patients.

Calcium channel blockers

Neurodegeneration in PD is influenced by a complex interplay of genetic and environmental factors, along with the selective vulnerability of specific neuronal populations, particularly dopaminergic neurons, in the substantia nigra (SN). However, the specific cell-autonomous mechanisms underlying this vulnerability remain unclear. Notably, neurons that depend on Ca(v)1.3 L-type calcium channels for maintaining autonomous pacemaking activity may be especially vulnerable to mitochondrial oxidative stress, suggesting that the inhibition of L-type calcium channels could confer neuroprotective benefits.[8] Furthermore, recent investigations have demonstrated that L-type, N-type, and T-type calcium channel blockers (CCBs) can inhibit the transmission of α-synuclein.[55] Isradipine, a dihydropyridine CCB with a strong affinity for L-type calcium channels that is approved for hypertension treatment, has exhibited neuropro-

tective effects in animal models of PD.[56,57] Additionally, epidemiological studies have suggested that various CCBs are associated with a significantly lower risk of future PD diagnosis.[12,58]

In light of these findings, a phase II randomized clinical trial was conducted to assess the tolerability of isradipine.[59] This trial established 10 mg daily as the maximum tolerable daily dose because higher doses are associated with adverse effects. Using this dosage, the STEADY-PD III trial, a large phase III multicenter, randomized, double-blind, placebo-controlled study, was initiated to evaluate the efficacy of isradipine in decelerating the progression of PD.[60] The trial enrolled 336 patients with drug-naïve early-stage PD and randomized them to receive either isradipine or a placebo for 36 months. The primary endpoint was the change in the Unified Parkinson's Disease Rating Scale (UPDRS) parts I to III score, measured in the on-medication state, from baseline to 36 months. The results showed that isradipine did not yield any significant benefits in terms of slowing clinical progression, and no significant differences were observed in either the primary or secondary outcome measures. The failure of the STEADY-PD III trial can be attributed to several key factors. First, the primary outcome measure (UPDRS score in the on-medication state) may not have been sensitive enough to detect disease-modifying effects, as symptomatic treatment could have masked subtle differences. Second, insufficient target engagement in the brain raises concerns about whether the administered dose effectively blocks L-type calcium channels, although higher doses are likely limited by side effects such as orthostatic hypotension. Finally, slow disease progression in the placebo group may have reduced the ability of the trial to detect meaningful differences, suggesting that longer follow-up or biomarker-based assessments might be necessary for future studies. However, a recent study indicated that the use of CCBs has a protective effect against conversion to dementia,[61] suggesting the need for further investigation of the potential beneficial effects of CCBs on the nonmotor symptoms of PD. Additionally, the secondary analysis of the phase II clinical trial suggested potential benefits.[62] These findings highlight the complexities of translating neuroprotective strategies from preclinical models to clinical practice and underscore the need for further research to better understand the role of CCBs in PD, particularly their potential effects on nonmotor symptoms and disease-modifying outcomes. Regrettably, no further research is currently being conducted on isradipine or other CCBs for PD.

Statins

Statins are widely prescribed not only for the primary and secondary prevention of cardiovascular diseases through the inhibition of cholesterol biosynthesis but also as potential neuroprotective agents in the context of neurological disorders owing to their various pleiotropic effects.[63] The impact of statin treatment on the pathogenesis of PD in experimental models, as well as its epidemiological association with PD incidence, remains highly contentious. Specifically, whereas preclinical investigations have indicated that statins may confer protective benefits against the aggregation of α-synuclein and the degeneration of dopaminergic neurons in PD,[64-66] some studies have reported adverse effects of atorvastatin and simvastatin on the survival of dopaminergic neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD.[67] Furthermore, epidemiological research has suggested that statins may be associated with a reduced incidence of PD[68,69]; however, observational studies conducted by Huang et al.[70,71] have posited that statins could negatively influence PD incidence by lowering cholesterol levels. Additionally, a recent investigation indicated that the use of statins may adversely affect baseline nigrostriatal dopamine degeneration and long-term motor and cognitive outcomes in individuals with PD.[72]

To date, only two clinical studies have examined the effects of statins on PD. A phase II trial using simvastatin, known as PD-STAT, enrolled 230 participants with moderate PD and assessed the daily administration of either 40 mg simvastatin or a placebo over two years. This study not only failed to demonstrate that simvastatin is effective in slowing the progression of PD but also showed worsening motor symptoms in the simvastatin-treated group,[73] leading to the discontinuation of further clinical research. Another nationwide phase II study in Taiwan using lovastatin enrolled 77 patients with early-stage PD, and lovastatin 80 mg or placebo was administered for 48 weeks with a 4-week wash-out period.[74] The MDS-UPDRS part III scores at 52 weeks were not significantly different between the two groups. Although it did not meet the primary outcome in the phase II clinical trial, it demonstrated a possible beneficial effect in terms of dopaminergic cell loss as assessed by ^{18}F-fluorodopa positron emission tomography, suggesting the potential for further research. These findings highlight the complex and conflicting nature of the effects of statins on PD, underscoring the need for further well-designed clinical studies to clarify their potential therapeutic roles and underlying mechanisms in PD.

Iron-chelating agents

Postmortem studies have demonstrated enormous iron accumulation in patients with PD.[75] Iron is associated with oxidative stress and ferroptosis (i.e., an iron-dependent form of cell death)[76]; moreover, it is believed to affect the proteasome, which subsequently modulates the clearance of aggregated α-synuclein.[77] Notably, deferiprone, an iron-chelating agent, can cross the blood-brain barrier. Specifically, previous in vitro and in vivo studies have shown that deferiprone treatment reduces

oxidative stress, improves motor symptoms, and increases striatal dopamine levels.[78] A preliminary study indicated that early intervention with deferiprone led to a reduction in nigral iron accumulation and an improvement in motor function in patients with early-stage PD.[78] Additionally, a randomized, double-blind, placebo-controlled trial demonstrated that a 6-month course of deferiprone was well tolerated and effectively decreased iron levels in specific regions of the brain.[79]

These findings encourage further exploration of iron chelators as potential therapeutic agents for PD. Recently, a multicenter, phase II, double-blind, randomized trial (FAIRPARK-II) investigated deferiprone in patients with newly diagnosed PD.[80] This trial enrolled 372 participants who had not received levodopa treatment and randomly assigned them to receive either deferiprone (15 mg/kg twice daily) or placebo for 36 weeks. Although magnetic resonance imaging scans confirmed reduced brain iron deposition in the deferiprone-treated group, the MDS-UPDRS part 3 scores unexpectedly worsened in this group compared with those in the placebo group. This divergence began at 3 months and persisted throughout the 9 months. Furthermore, no difference in dopamine transporter density was observed between the groups, suggesting that iron chelation therapy does not have disease-modifying effects. Recent investigations have also evaluated the efficacy of deferiprone in patients with newly diagnosed and early-stage PD using the SKY and EMBARK studies. The SKY study, which included patients with early-stage PD receiving stable dopaminergic therapy, revealed no significant benefit of deferiprone in improving motor symptoms, except for a nonsignificant trend toward improvement at a dose of 600 mg twice daily. Conversely, the EMBARK study, which examined treatment-naive and dopaminergic-treated patients, revealed a significant worsening of motor symptoms in the treatment-naive group; however, the dopaminergic-treated group exhibited no significant motor improvements. Both studies concluded that deferiprone does not provide substantial motor function benefits in patients with PD and highlighted the potential risks when it is used without concurrent dopaminergic therapy.[81]

Abelson murine leukemia viral homolog 1 inhibitors

Abelson murine leukemia viral homolog 1 (c-Abl) tyrosine kinase performs various biological functions, including regulating synapse formation, neurite outgrowth, and neurogenesis in the central nervous system.[82] Interestingly, c-Abl activation increases with age and is elevated in specific brain regions of patients with PD, as well as in PD animal models. This aberrant activation has been linked to the phosphorylation of α-synuclein at tyrosine 39 and serine 125, leading to α-synuclein aggregation.[83] Nilotinib, which is an inhibitor of c-Abl tyrosine kinase, has shown promise in preclinical PD models. In the MPTP mouse model of PD, nilotinib reduced c-Abl activation, preserved dopamine neurons, and mitigated behavioral deficits.[84] Notably, a preliminary study involving 12 patients with advanced PD demonstrated mild improvements in motor and cognitive functions after 24 weeks of treatment, which were reversed by 36 weeks.[85] Although these findings generated enthusiasm, their interpretation was limited by the study's small size, lack of a control group, and potential confounding effects, such as monoamine oxidase-B inhibitor withdrawal, influencing biomarker changes such as increased CSF homovanillic acid levels.[86]

Since then, two randomized phase II clinical trials have investigated the safety and tolerability of nilotinib at daily doses of 150 mg and 300 mg compared with placebo.[87] A single-center study with 75 participants reported increased dopamine metabolite levels in the CSF in some nilotinib-treated groups but reported no significant differences in motor or nonmotor outcomes. However, this study was not designed to evaluate its efficacy. Although adverse events were comparable between the groups, serious adverse events, including four cardiovascular events, occurred more frequently in nilotinib-treated patients. A larger multicenter trial (NILO-PD) with a similar design produced conflicting findings,[88] demonstrating the poor central nervous system penetration of nilotinib and no changes in dopamine metabolites.

These conflicting outcomes raise questions regarding the feasibility of pursuing further trials of nilotinib for PD. Additionally, although the final results have not yet been published, a recently conducted phase II trial using vodobatinib in early-stage PD reported that this novel c-Abl inhibitor did not show any evidence of treatment benefits in patients with PD.

Memantine

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has garnered attention for its potential role in PD, particularly through the modulation of α-synuclein transmission. Experimental evidence highlights that NMDA receptors play crucial roles in facilitating the cell-to-cell propagation of α-synuclein aggregates.[89] In vitro and in vivo studies have demonstrated that memantine effectively inhibits this transmission, suggesting its potential as a disease-modifying agent in PD.[90]

Clinically, memantine has been evaluated for its effects on cognitive and behavioral symptoms in PD dementia and DLB. A pivotal randomized controlled trial reported that memantine led to significant improvements in behavioral symptoms, including reduced agitation and aggression, in patients with DLB. However, their effects on global cognition are modest and variable. Furthermore, in patients with PD dementia, memantine tends to improve cognitive function, particularly in domains such as attention and executive function. However, the results did not

reach statistical significance.[91] Despite these promising outcomes, subsequent meta-analyses have raised questions about the robustness of these findings, particularly in placebo-controlled trials, where the observed benefits for cognition were minimal compared with those of open-label studies.[92] Consequently, current guidelines do not recommend memantine for routine use in improving cognitive function in patients with PD. Nevertheless, experimental studies suggesting its ability to inhibit α-synuclein propagation provide a rationale for exploring memantine as a disease-DMT for PD.[89,90] This hypothesis is currently under investigation in an ongoing clinical trial (ID: NCT03858270) that aims to assess the impact of memantine on slowing disease progression through the modulation of α-synuclein dynamics.

RECENTLY UPDATED LIST OF PRIORITIZED CANDIDATE DRUGS

Fasudil

Fasudil, a Rho-associated protein kinase (ROCK) inhibitor, has garnered attention as a potential therapeutic agent for PD owing to its multifaceted neuroprotective mechanisms. Fasudil has a unique ability to modulate pathological α-synuclein aggregation through both direct and indirect pathways, making it a promising candidate for clinical exploration. In particular, fasudil directly binds to the C-terminal region of α-synuclein, specifically targeting tyrosine residues Y133 and Y136, as revealed by nuclear magnetic resonance spectroscopy. This interaction disrupts α-synuclein aggregation, delays amyloid fibril formation, and reduces the accumulation of toxic high-molecular-weight aggregates. In vitro studies in H4 human neuroglioma cells and cell-free aggregation assays revealed significant anti-aggregation effects at micromolar concentrations.[93] Notably, long-term administration of fasudil in transgenic mouse models of PD (e.g., α-SynA53T mice) not only attenuated α-synuclein aggregation but also improved motor and cognitive functions.[94] Behavioral assays, such as CatWalk gait analysis and novel object recognition tests, demonstrated significant recovery, elucidating the potential of fasudil to modify disease progression. Furthermore, immunohistochemical analysis revealed reduced α-synuclein levels in the SN. In addition to its direct effects on α-synuclein, fasudil inhibition by ROCK contributes to its neuroprotective profile. ROCK inhibition has been shown to enhance regenerative sprouting, mitigate dopaminergic neuronal death, and reduce neuroinflammation in toxin-induced PD models.[95] These complementary pathways strengthen the potential of fasudil as a multifaceted DMT.

Moreover, the dual ability of fasudil to directly target α-synuclein aggregation and modulate neuroinflammatory and regenerative pathways via ROCK inhibition provides a strong mechanistic basis for its clinical application in PD. The translational potential of fasudil, demonstrated by its efficacy in both in vitro and in vivo models, supports its use in ongoing clinical trials aimed at evaluating its safety, tolerability, and therapeutic efficacy in slowing PD progression.[96]

β2-adrenergic receptor agonists

β2-adrenergic receptor (β2AR) agonists have emerged as promising candidates for repurposing in PD due to their role in modulating α-synuclein expression. Mechanistically, β2AR activation reduces *SNCA* transcription through epigenetic regulation, specifically by decreasing histone histone 3 lysine 27 acetylation at the *SNCA* promoter and enhancer regions. Notably, preclinical studies have demonstrated that β2AR agonists, such as salbutamol and clenbuterol, can lower *SNCA* expression, reduce alpha-synuclein protein aggregation, and protect dopaminergic neurons from neurotoxin-induced degeneration.[97] Moreover, epidemiological analyses have further supported this potential, with longitudinal data from the Norwegian Prescription Database showing a reduced PD risk among salbutamol users (rate ratio: 0.66).[97] Additionally, a meta-analysis reported a pooled adjusted risk ratio of 0.87 for PD among β2AR agonist users, suggesting a modest but consistent protective effect.[98]

As mentioned previously, the ACTRN12620000560998 trial in Australia investigated the neuroprotective effects of albuterol in individuals with early PD, focusing on the ability of β2AR agonists to reduce alpha-synuclein pathology and modulate disease progression. These efforts highlight the growing recognition of β2AR agonists as potential disease-modifying agents, offering a novel approach for targeting the underlying molecular pathology of PD.

Terazosin

Impaired energy metabolism and bioenergetic deficits are crucial for PD pathogenesis.[99] In this context, terazosin, an α1-adrenergic receptor antagonist with the unique ability to increase glycolysis by activating phosphoglycerate kinase 1 (PGK1), has emerged as a promising candidate for disease modification in PD.[100]

Terazosin binds to PGK1, the first adenosine triphosphate (APT)-producing enzyme involved in glycolysis, thereby stimulating its activity and increasing ATP production. This mechanism has been demonstrated in preclinical models and patient-derived data, suggesting that terazosin addresses the bioenergetic deficits observed in PD.[100] Furthermore, in toxin-induced and genetic models of PD, including MPTP-treated mice and α-synuclein-overexpressing systems, terazosin increased brain ATP levels, prevented dopaminergic neuron loss, and mitigated motor

dysfunction. In another study, terazosin prevented cognitive decline in animal models in which dopamine was depleted in the ventral tegmental area.[101]

In terms of clinical evidence, data from large-scale pharmacoepidemiologic studies suggest that terazosin and related glycolysis-enhancing drugs (e.g., doxazosin and alfuzosin) are associated with slower progression of motor symptoms and a reduced hazard of developing cognitive impairments and PD-related dementia.[100] In addition, analyses of large health care databases, such as the Danish Nationwide Health Registries and MarketScan, demonstrated a reduced risk of developing PD in patients using a glycolysis-enhancing α1-blocker compared with tamsulosin, a similar α1-blocker without glycolysis-enhancing effects.[102] Importantly, the dose-response relationships observed in this study further support a protective association. Finally, a 12-week pilot study evaluating terazosin in patients with PD demonstrated significant increases in brain and blood ATP levels, suggesting successful target engagement.[103] Although the study was not powered to evaluate its clinical efficacy, these findings support the hypothesis that increased glycolysis may modify disease progression.

SGLT-2 inhibitors

Emerging evidence suggests that SGLT-2 inhibitors, a class of oral antidiabetic drugs, possess antioxidative and mitochondrial protective properties, potentially offering neuroprotective benefits.[104] For example, dapagliflozin, an SGLT-2 inhibitor, has demonstrated neuroprotective effects in a rotenone-induced PD animal model, improving motor function, decreasing α-synuclein expression, and increasing dopamine and tyrosine hydroxylase levels, suggesting its potential to increase dopaminergic activity.[105] Furthermore, empagliflozin, another SGLT-2 inhibitor, exhibited restorative effects in a rotenone-induced PD rat model, enhancing motor function, as assessed by open field tests, grip strength assessments, and footprint gait analysis, while preserving neuronal integrity. Empagliflozin was found to reduce astrogliosis and microgliosis, decrease immunostaining for glial fibrillary acidic protein and ionized calcium-binding adaptor protein 1, and modulate the GRP78/PERK/eIF2α/CHOP ER stress pathway.[106] Additionally, empagliflozin downregulated miR-211-5p, diminished oxidative stress, and reduced the activation of astrocytes and microglia, as well as neuroinflammation, while promoting autophagy. These encouraging preclinical results highlight the necessity for further investigation of these agents in clinical trials, with dapagliflozin currently being assessed in clinical studies (ID: NCT06263673).

CONCLUSION

Given the significant burden of this neurodegenerative disorder on patients and the health care system, DMTs for PD remain a priority. Drug repositioning and repurposing offer a pragmatic and efficient pathway to address the unmet need for therapies that can slow or arrest disease progression. Promising candidates, such as GLP-1 receptor agonists, DPP-4 inhibitors, and ambroxol, have demonstrated potential through their diverse mechanisms of action, targeting key pathological features of PD, including α-synuclein aggregation, neuroinflammation, lysosomal dysfunction, and oxidative stress. However, the challenges faced in drug repurposing trials for PD highlight the need for more strategic approaches to improve success rates. First, refining outcome measures is essential, as traditional clinical scales may not effectively capture disease-modifying effects. Integrating biomarkers such as imaging markers or fluid-based biomarkers can provide more objective assessments of disease progression. Second, validating target engagement before large-scale trials is critical to ensure that repurposed drugs effectively reach and modulate their intended targets in the brain. Molecular imaging and pharmacodynamic biomarkers can play crucial roles in confirming this early. Third, optimizing dosing strategies is also important, as many repurposed drugs may require careful dose adjustments to balance efficacy with tolerability. Longer and adaptive clinical trial designs should be considered, allowing for flexible adjustments based on emerging data and enabling trials to capture subtle disease progression over extended periods. Finally, advancing precision medicine approaches, such as patient stratification based on genetic, biomarker, or disease progression profiles, can help identify subgroups more likely to benefit from specific repurposed drugs. By integrating these strategies, future drug repurposing trials for PD can be designed more effectively, increasing the likelihood of identifying successful disease-DMTs.

Collaborative efforts among academia, industry, and regulatory agencies are essential for optimizing clinical trial designs, refining target populations, and integrating biomarker-driven approaches. By leveraging advances in molecular biology, data analytics, and personalized medicine, this field can address the multifaceted challenges of PD drug development. Although the setbacks in phase III trials highlight the difficulties inherent in this endeavor, they also provide critical insights for refining future strategies. With continued innovation and commitment, drug repurposing and repositioning hold significant promise for transforming the treatment landscape of PD, ultimately improving the outcomes and quality of life of millions of patients worldwide.

Conflicts of Interest

The authors have no financial conflicts of interest.

Funding Statement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. RS-2023-00209580).

Acknowledgments

Medical Illustration & Design (MID), as a member of the Medical Research Support Services of Yonsei University College of Medicine, providing excellent support with medical illustration.

Author Contributions

Conceptualization: Seong Ho Jeong, Phil Hyu Lee. Data curation: Seong Ho Jeong. Funding acquisition: Seong Ho Jeong. Investigation: Seong Ho Jeong, Phil Hyu Lee. Project administration: Seong Ho Jeong, Phil Hyu Lee. Resources: Seong Ho Jeong, Phil Hyu Lee. Software: Seong Ho Jeong. Supervision: Phil Hyu Lee. Validation: Phil Hyu Lee. Visualization: Seong Ho Jeong. Writing—original draft: Seong Ho Jeong. Writing—review & editing: Phil Hyu Lee.

ORCID iDs

Seong Ho Jeong https://orcid.org/0000-0003-4439-4390
Phil Hyu Lee https://orcid.org/0000-0001-9931-8462

REFERENCES

1. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet 2021;397:2284-2303.
2. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology 2009;72(21 Suppl 4):S1-S136.
3. Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med 2020;36:1-12.
4. Uemura N, Uemura MT, Luk KC, Lee VM, Trojanowski JQ. Cell-to-cell transmission of tau and α-synuclein. Trends Mol Med 2020;26:936-952.
5. 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 Parkinsons Dis 2024;14:899-912.
6. Mahlknecht P, Seppi K, Poewe W. The concept of prodromal Parkinson's disease. J Parkinsons Dis 2015;5:681-697.
7. Marek K, Chowdhury S, Siderowf A, Lasch S, Coffey CS, Caspell-Garcia C, et al. The Parkinson's progression markers initiative (PPMI) - establishing a PD biomarker cohort. Ann Clin Transl Neurol 2018;5:1460-1477.
8. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. Nat Rev Neurosci 2017;18:101-113.
9. Langedijk J, Mantel-Teeuwisse AK, Slijkerman DS, Schutjens MH. Drug repositioning and repurposing: terminology and definitions in literature. Drug Discov Today 2015;20:1027-1034.
10. Hubsher G, Haider M, Okun MS. Amantadine: the journey from fighting flu to treating Parkinson disease. Neurology 2012;78:1096-1099.
11. Scott TJ, O'Connor AC, Link AN, Beaulieu TJ. Economic analysis of opportunities to accelerate Alzheimer's disease research and development. Ann N Y Acad Sci 2014;1313:17-34.
12. Becker C, Jick SS, Meier CR. Use of antihypertensives and the risk of Parkinson disease. Neurology 2008;70(16 Pt 2):1438-1444.
13. Brauer R, Wei L, Ma T, Athauda D, Girges C, Vijiaratnam N, et al. Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes. Brain 2020;143:3067-3076.
14. 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:e000535.
15. Hideshima M, Kimura Y, Aguirre C, Kakuda K, Takeuchi T, Choong CJ, et al. Two-step screening method to identify α-synuclein aggregation inhibitors for Parkinson's disease. Sci Rep 2022;12:351.
16. Fletcher EJR, Kaminski T, Williams G, Duty S. Drug repurposing strategies of relevance for Parkinson's disease. Pharmacol Res Perspect 2021;9:e00841.
17. Wyse RK, Isaacs T, Barker RA, Cookson MR, Dawson TM, Devos D, et al. Twelve years of drug prioritization to help accelerate disease modification trials in Parkinson's disease: the international linked clinical trials initiative. J Parkinsons Dis 2024;14:657-666.
18. Oprea TI, Overington JP. Computational and practical aspects of drug repositioning. Assay Drug Dev Technol 2015;13:299-306.
19. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-1705.
20. Parkes DG, Mace KF, Trautmann ME. Discovery and development of exenatide: the first antidiabetic agent to leverage the multiple benefits of the incretin hormone, GLP-1. Expert Opin Drug Discov 2013;8:219-244.
21. Athauda D, Foltynie T. The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action. Drug Discov Today 2016;21:802-818.
22. Athauda D, Foltynie T. Insulin resistance and Parkinson's disease: a new target for disease modification? Prog Neurobiol 2016;145-146:98-120.
23. Harkavyi A, Abuirmeileh A, Lever R, Kingsbury AE, Biggs CS, Whitton PS. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. J Neuroinflammation 2008;5:19.
24. Liu W, Jalewa J, Sharma M, Li G, Li L, Hölscher C. Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. Neuroscience 2015;303:42-50.
25. Yun SP, Kam TI, Panicker N, Kim S, Oh Y, Park JS, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. Nat Med 2018;24:931-938.
26. 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 Invest 2013;123:2730-2736.
27. 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;390:1664-1675.
28. 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;390:1176-1185.
29. 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;23:37-45.
30. Malatt C, Wu T, Bresee C, Hogg E, Wertheimer 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;98:3068.
31. Wu YQ, Limburg DC, Wilkinson DE, Jackson P, Steiner JP, Hamilton GS, et al. Neuroprotective effects of inhibitors of dipeptidyl peptidase-iV in vitro and in vivo. Adv Exp Med Biol 2003;524:351-355.
32. Abhangi KV, Patel JI. Neuroprotective effects of linagliptin in a rotenone-induced rat model of Parkinson's disease. Indian J Pharmacol 2022;54:46-50.
33. Badawi GA, Abd El Fattah MA, Zaki HF, El Sayed MI. Sitagliptin and liraglutide reversed nigrostriatal degeneration of rodent brain in rotenone-induced Parkinson's disease. Inflammopharmacology 2017;25:369-382.

34. Abdelsalam RM, Safar MM. Neuroprotective effects of vildagliptin in rat rotenone Parkinson's disease model: role of RAGE-NFκB and Nrf2-antioxidant signaling pathways. J Neurochem 2015;133:700-707.
35. Nassar NN, Al-Shorbagy MY, Arab HH, Abdallah DM. Saxagliptin: a novel antiparkinsonian approach. Neuropharmacology 2015;89:308-317.
36. Dai Y, Dai D, Wang X, Ding Z, Mehta JL. DPP-4 inhibitors repress NLRP3 inflammasome and interleukin-1beta via GLP-1 receptor in macrophages through protein kinase C pathway. Cardiovasc Drugs Ther 2014;28:425-432.
37. Yazbeck R, Howarth GS, Abbott CA. Dipeptidyl peptidase inhibitors, an emerging drug class for inflammatory disease? Trends Pharmacol Sci 2009;30:600-607.
38. Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other? Int J Clin Pract 2014;68:557-567.
39. Svenningsson P, Wirdefeldt K, Yin L, Fang F, Markaki I, Efendic S, et al. Reduced incidence of Parkinson's disease after dipeptidyl peptidase-4 inhibitors—a nationwide case-control study. Mov Disord 2016;31:1422-1423.
40. Lin YH, Hsu CC, Liu JS, Chang KC, Huang JA. Use of dipeptidyl peptidase-4 inhibitors was associated with a lower risk of Parkinson's disease in diabetic patients. Sci Rep 2023;13:22489.
41. Jeong SH, Chung SJ, Yoo HS, Hong N, Jung JH, Baik K, et al. Beneficial effects of dipeptidyl peptidase-4 inhibitors in diabetic Parkinson's disease. Brain 2021;144:1127-1137.
42. Kim NH, Yu T, Lee DH. The nonglycemic actions of dipeptidyl peptidase-4 inhibitors. Biomed Res Int 2014;2014:368703.
43. Hu Y, Xu J, Wang J, Zhu L, Wang J, Zhang Q. DPP-4 inhibitors suppress tau phosphorylation and promote neuron autophagy through the AMPK/mTOR pathway to ameliorate cognitive dysfunction in diabetic mellitus. ACS Chem Neurosci 2023;14:3335-3346.
44. Maegawa GH, Tropak MB, Buttner JD, Rigat BA, Fuller M, Pandit D, et al. Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease. J Biol Chem 2009;284:23502-23516.
45. Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361:1651-1661.
46. Maor G, Rencus-Lazar S, Filocamo M, Steller H, Segal D, Horowitz M. Unfolded protein response in Gaucher disease: from human to Drosophila. Orphanet J Rare Dis 2013;8:140.
47. Beavan MS, Schapira AH. Glucocerebrosidase mutations and the pathogenesis of Parkinson disease. Ann Med 2013;45:511-521.
48. Migdalska-Richards A, Ko WKD, Li Q, Bezard E, Schapira AHV. Oral ambroxol increases brain glucocerebrosidase activity in a nonhuman primate. Synapse 2017;71:e21967.
49. Migdalska-Richards A, Daly L, Bezard E, Schapira AH. Ambroxol effects in glucocerebrosidase and α-synuclein transgenic mice. Ann Neurol 2016;80:766-775.
50. McNeill A, Magalhaes J, Shen C, Chau KY, Hughes D, Mehta A, et al. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain 2014;137(Pt 5):1481-1495.
51. Maor G, Cabasso O, Krivoruk O, Rodriguez J, Steller H, Segal D, et al. The contribution of mutant GBA to the development of Parkinson disease in Drosophila. Hum Mol Genet 2016;25:2712-2727.
52. 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;77:427-434.
53. 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;19:20.
54. Chwiszczuk LJ, Breitve MH, Kirsebom BB, Selnes P, Fløvig JC, Knapskog AB, et al. The ANeED study - ambroxol in new and early dementia with Lewy bodies (DLB): protocol for a phase IIa multicentre, randomised, double-blinded and placebo-controlled trial. Front Aging Neurosci 2023;15:1163184.
55. Ueda J, Uemura N, Ishimoto T, Taguchi T, Sawamura M, Nakanishi E, et al. Ca2+–calmodulin–calcineurin signaling modulates α-synuclein transmission. Mov Disord 2023;38:1056-1067.
56. 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;43:364-371.
57. Chan CS, Guzman JN, Ilijic E, Mercer JN, Rick C, Tkatch T, et al. 'Rejuvenation' protects neurons in mouse models of Parkinson's disease. Nature 2007;447:1081-1086.
58. 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;67:600-606.
59. Parkinson Study Group. Phase II safety, tolerability, and dose selection study of isradipine as a potential disease-modifying intervention in early Parkinson's disease (STEADY-PD). Mov Disord 2013;28:1823-1831.
60. Parkinson Study Group STEADY-PD III Investigators. Isradipine versus placebo in early Parkinson disease: a randomized trial. Ann Intern Med 2020;172:591-598.
61. Jung JH, Na HK, Jeong SH, Chung SJ, Yoo HS, Lee YH, et al. Effects of dihydropyridines on the motor and cognitive outcomes of patients with Parkinson's disease. Mov Disord 2023;38:843-853.
62. 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;37:334-342.
63. Moon GJ, Kim SJ, Cho YH, Ryoo S, Bang OY. Antioxidant effects of statins in patients with atherosclerotic cerebrovascular disease. J Clin Neurol 2014;10:140-147.
64. Bar-On P, Crews L, Koob AO, Mizuno H, Adame A, Spencer B, et al. Statins reduce neuronal α-synuclein aggregation in in vitro models of Parkinson's disease. J Neurochem 2008;105:1656-1667.
65. Kumar A, Sharma N, Gupta A, Kalonia H, Mishra J. Neuroprotective potential of atorvastatin and simvastatin (HMG-CoA reductase inhibitors) against 6-hydroxydopamine (6-OHDA) induced Parkinson-like symptoms. Brain Res 2012;1471:13-22.
66. Yan J, Sun J, Huang L, Fu Q, Du G. Simvastatin prevents neuroinflammation by inhibiting N-methyl-D-aspartic acid receptor 1 in 6-hydroxydopamine-treated PC12 cells. J Neurosci Res 2014;92:634-640.
67. Kreisler A, Gelé P, Wiart JF, Lhermitte M, Destée A, Bordet R. Lipid-lowering drugs in the MPTP mouse model of Parkinson's disease: fenofibrate has a neuroprotective effect, whereas bezafibrate and HMG-CoA reductase inhibitors do not. Brain Res 2007;1135:77-84.
68. Lee YC, Lin CH, Wu RM, Lin MS, Lin JW, Chang CH, et al. Discontinuation of statin therapy associates with Parkinson disease: a population-based study. Neurology 2013;81:410-416.
69. Wahner AD, Bronstein JM, Bordelon YM, Ritz B. Statin use and the risk of Parkinson disease. Neurology 2008;70(16 Pt 2):1418-1422.
70. Huang X, Alonso A, Guo X, Umbach DM, Lichtenstein ML, Ballantyne CM, et al. Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study. Mov Disord 2015;30:552-559.
71. Huang X, Sterling NW, Du G, Sun D, Stetter C, Kong L, et al. Brain cholesterol metabolism and Parkinson's disease. Mov Disord 2019;34:386-395.
72. Jeong SH, Lee HS, Chung SJ, Yoo HS, Jung JH, Baik K, et al. Effects of statins on dopamine loss and prognosis in Parkinson's disease. Brain 2021;144:3191-3200.
73. 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;79:1232-1241.
74. Lin CH, Chang CH, Tai CH, Cheng MF, Chen YC, Chao YT, et al. A double-blind, randomized, controlled trial of lovastatin in early-stage Parkinson's disease. Mov Disord 2021;36:1229-1237.
75. Moreau C, Duce JA, Rascol O, Devedjian JC, Berg D, Dexter D, et al. Iron

as a therapeutic target for Parkinson's disease. Mov Disord 2018;33:568-574.
76. Guiney SJ, Adlard PA, Bush AI, Finkelstein DI, Ayton S. Ferroptosis and cell death mechanisms in Parkinson's disease. Neurochem Int 2017;104:34-48.
77. Chen B, Wen X, Jiang H, Wang J, Song N, Xie J. Interactions between iron and α-synuclein pathology in Parkinson's disease. Free Radic Biol Med 2019;141:253-260.
78. 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;21:195-210.
79. 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;7:1398.
80. 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;387:2045-2055.
81. Devos D, Rascol O, Meissner WG, Foubert-Samier A, Lewis S, Tranchant C, et al. Therapeutic modalities of deferiprone in Parkinson's disease: SKY and EMBARK studies. J Parkinsons Dis 2024 Dec 27 [Epub]. Available from: http://doi.org/10.1177/1877718X241300295.
82. Brahmachari S, Karuppagounder SS, Ge P, Lee S, Dawson VL, Dawson TM, et al. c-Abl and Parkinson's disease: mechanisms and therapeutic potential. J Parkinsons Dis 2017;7:589-601.
83. Brahmachari S, Ge P, Lee SH, Kim D, Karuppagounder SS, Kumar M, et al. Activation of tyrosine kinase c-Abl contributes to α-synuclein-induced neurodegeneration. J Clin Invest 2016;126:2970-2988.
84. Karuppagounder SS, Brahmachari S, Lee Y, Dawson VL, Dawson TM, Ko HS. The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci Rep 2014;4:4874.
85. Pagan F, Hebron M, Valadez EH, Torres-Yaghi Y, Huang X, Mills RR, et al. Nilotinib effects in Parkinson's disease and dementia with Lewy bodies. J Parkinsons Dis 2016;6:503-517.
86. Schwarzschild MA. Could MAO-B inhibitor withdrawal rather than nilotinib benefit explain the dopamine metabolite increase in parkinsonian study subjects? J Parkinsons Dis 2017;7:79-80.
87. Pagan FL, Hebron ML, Wilmarth B, Torres-Yaghi Y, Lawler A, Mundel EE, et al. Nilotinib effects on safety, tolerability, and potential biomarkers in Parkinson disease: a phase 2 randomized clinical trial. JAMA Neurol 2020;77:309-317.
88. Simuni T, Fiske B, Merchant K, Coffey CS, Klingner E, Caspell-Garcia C, et al. Efficacy of nilotinib in patients with moderately advanced Parkinson disease: a randomized clinical trial. JAMA Neurol 2021;78:312-320.
89. Oh SH, Kim HN, Park HJ, Shin JY, Bae EJ, Sunwoo MK, et al. Mesenchymal stem cells inhibit transmission of α-synuclein by modulating clathrin-mediated endocytosis in a parkinsonian model. Cell Rep 2016;14:835-849.
90. Lee JE, Kim HN, Kim DY, Shin YJ, Shin JY, Lee PH. Memantine exerts neuroprotective effects by modulating α-synuclein transmission in a parkinsonian model. Exp Neurol 2021;344:113810.
91. Emre M, Tsolaki M, Bonuccelli U, Destée A, Tolosa E, Kutzelnigg A, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:969-977.
92. Brennan L, Pantelyat A, Duda JE, Morley JF, Weintraub D, Wilkinson JR, et al. Memantine and cognition in Parkinson's disease dementia/dementia with Lewy bodies: a meta-analysis. Mov Disord Clin Pract 2015;3:161-167.
93. Robustelli P, Ibanez-de-Opakua A, Campbell-Bezat C, Giordanetto F, Becker S, Zweckstetter M, et al. Molecular basis of small-molecule binding to α-synuclein. J Am Chem Soc 2022;144:2501-2510.
94. Tatenhorst L, Eckermann K, Dambeck V, Fonseca-Ornelas L, Walle H, Lopes da Fonseca T, et al. Fasudil attenuates aggregation of α-synuclein in models of Parkinson's disease. Acta Neuropathol Commun 2016;4:39.
95. Iyer M, Subramaniam MD, Venkatesan D, Cho SG, Ryding M, Meyer M, et al. Role of RhoA-ROCK signaling in Parkinson's disease. Eur J Pharmacol 2021;894:173815.
96. Wolff AW, Bidner H, Remane Y, Zimmer J, Aarsland D, Rascol O, et al. Protocol for a randomized, placebo-controlled, double-blind phase IIa study of the safety, tolerability, and symptomatic efficacy of the ROCK-inhibitor Fasudil in patients with Parkinson's disease (ROCK-PD). Front Aging Neurosci 2024;16:1308577.
97. 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;357:891-898.
98. Singh A, Hussain S, Akkala S, Klugarová J, Pokorná A, Klugar M, et al. Beta-adrenergic drugs and risk of Parkinson's disease: a systematic review and meta-analysis. Ageing Res Rev 2022;80:101670.
99. Schapira AH. Mitochondria in the aetiology and pathogenesis of Parkinson's disease. Lancet Neurol 2008;7:97-109.
100. 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 Invest 2019;129:4539-4549.
101. 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;9:32.
102. 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;78:407-413.
103. 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.
104. Lin KJ, Wang TJ, Chen SD, Lin KL, Liou CW, Lan MY, et al. Two birds one stone: the neuroprotective effect of antidiabetic agents on Parkinson disease-focus on sodium-glucose cotransporter 2 (SGLT2) inhibitors. Antioxidants (Basel) 2021;10:1935.
105. Arab HH, Safar MM, Shahin NN. Targeting ROS-dependent AKT/GSK-3β/NF-κB and DJ-1/Nrf2 pathways by dapagliflozin attenuates neuronal injury and motor dysfunction in rotenone-induced Parkinson's disease rat model. ACS Chem Neurosci 2021;12:689-703.
106. Motawi TK, Al-Kady RH, Abdelraouf SM, Senousy MA. Empagliflozin alleviates endoplasmic reticulum stress and augments autophagy in rotenone-induced Parkinson's disease in rats: targeting the GRP78/PERK/eIF2α/CHOP pathway and miR-211-5p. Chem Biol Interact 2022;362:110002.