

## **Drug repurposing in Parkinson's disease**

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### **Abstract**

The development of an intervention to slow or halt disease progression remains the greatest unmet therapeutic need in Parkinson's disease. Given the number of failures of various novel interventions in disease-modifying clinical trials in combination with ever increasing and lengthy drug development costs, attention is being turned to utilising existing compounds approved for other indications as novel treatments in Parkinson's disease.

Advances in rational and systemic drug repurposing has identified a number of drugs with potential benefits for Parkinson's disease pathology and offers a potentially quicker route to drug discovery. Here, we review the safety and potential efficacy of the most promising candidates repurposed as potential disease-modifying treatments for Parkinson's disease in the advanced stages of clinical testing.

### **Running head: Drug repurposing in Parkinson's disease**

#### **Key points:**

- **Disease modifying treatments are a great unmet need in Parkinson's disease**
- **Drug repurposing represents a potentially more efficient, less costly route to drug discovery.**

- **Current candidates being evaluated for repurposing in Parkinson's disease have helped identify potential new therapeutic targets**

## 1. Introduction

Parkinson's disease (PD) affects 6 million people worldwide. As an age-related neurodegenerative disease and with longevity increasing in most Western countries, this figure is estimated to increase to around 10 million by 2030 [1]. As well as the immense social impact on patients and their caregivers, it is estimated the economic burden of PD is \$14.4 billion per year in the USA [2], with increasing costs heavily weighted towards the more advanced features of the disease such as the development of cognitive impairment, non-motor symptoms, gait abnormalities and falls. Currently available symptomatic treatments for PD primarily focus on stimulation of dopaminergic signalling and can provide symptomatic relief for a limited time, however they have little effect on non-motor symptoms and none have been shown to affect the progressive pathological and clinical decline. Thus, alongside the need to develop more effective symptomatic therapies for PD, the greatest unmet need for patients, caregivers and healthcare systems, is the development of a disease modifying treatment for PD.

The exact pathophysiological mechanisms underlying neurodegeneration in PD are not well understood. However, disruption of cell-autonomous processes involved in modulation of protein folding and aggregation, and non-cell autonomous processes involving mitochondrial function, oxidative stress and inflammation are all thought to be implicated and have provided possible targets for therapeutic intervention and emphasise the need for a broader treatment approach [3,4].

Unfortunately, de novo drug discovery and development in PD is a lengthy, expensive and risky process. The estimated cost of bringing a new drug to market, from conception and basic research through to clinical testing and regulatory approval is approximately 2.6 billion dollars [5] and takes an average of 13-15 years [6]. Furthermore, it is estimated that only 10% of compounds make it through development to obtain approval by the European and/or the US regulatory authorities [7] while figures released from 2013 FDA New Drug Summary report indicate that despite a massive increase in R&D spending by pharmaceutical companies, the number of new molecular entities (NME's) approved per year has remained static for the past decade. It is therefore perhaps unsurprising that drug companies are facing a paradigm shift (not necessarily voluntarily) in how drugs are discovered and developed [8].

One method that pharmaceutical companies are increasingly turning to, to reverse the trend of high rates of attrition in drug development is to explore drug repurposing (also known as repositioning or reprofiling). This is the application of an existing drug to a new therapeutic use outside its original clinical indication [9]. Starting

with a compound that already has extensive human pharmacokinetic and safety data, allows pharmaceutical companies to bypass the long and costly pre-clinical stages required to advance a treatment to clinical trials and also opens up a drug development route available to academic centres and not-for-profit organisations. Success rates utilising drug repurposing have been reported to approach 30% [8], a vast improvement on traditional routes of drug discovery and has led to numerous successes across many different areas including cardiovascular disease, erectile dysfunction, cancer and irritable bowel syndrome [9]. Amantadine, originally developed in the 1960's as a prophylactic against several forms of influenza has since been approved for the treatment of motor complications in PD. Although approval for amantadine as a treatment for PD followed several appropriately designed large clinical trials, the impetus for the investigation of amantadine as a treatment for PD occurred as a result of a single doctor-patient interaction[10]. Historically, serendipitous clinical observations have identified possible drugs for repurposing but recently, more rational, systemic approaches for identifying and screening potential drugs for repurposing are increasingly being utilised. Creating open access databases detailing information on the structure and mechanism of action of individual drugs increases the opportunities for identifying potential compounds for repurposing [13]. In addition the creation of initiatives such as The National Centre for Advancing Translational Sciences (NCATS) Pharmaceutical Collection and the European Lead Factory has allowed the sharing of commercial compound libraries for collaborative public-private partnerships [14]. Similarly novel computational approaches based on analysing similarities between diseases, drugs, protein-protein interaction networks (PPIN) of genes, common adverse effects and combinations of drug-target interactions are identifying more potential opportunities for repurposing [15,16]. These methods have already been used to identify potential drugs for repurposing to address levodopa-induced dyskinesia, a common and often debilitating adverse effect of dopaminergic medication [11]. The development of novel symptomatic medications to treat PD is reviewed elsewhere [12] and this review will primarily address candidates evaluated for potential disease-modifying properties.

The creation of collaborative scientific networks to share and evaluate experimental data has also been valuable for identifying candidate drugs for repurposing opportunities. In 2001, the National Institute of Neurological Disorders and Stroke (NINDS) organized the Committee to Identify Neuroprotective Agents for Parkinson's (CINAPS). This was a group comprised of experts in PD, clinical trials, and clinical pharmacology, that solicited suggestions from academia, industry, clinicians in practice, and from the lay community to identify drugs that could be repurposed to slow disease progression in PD[17]. Among other criteria, drugs were evaluated in respect to availability of human safety data, evidence of blood-brain-barrier penetration, potential

mechanism and efficacy in pre-clinical models. In parallel, NINDS created the NIH Exploratory Trials in PD (NET-PD) program, a network of clinical sites, where agents identified by CINAPS could be tested in 1-year futility trials. These trials were designed primarily to rapidly screen agents and identify compounds unlikely to have therapeutic benefit, and minimise the risk of taking potentially ineffective agents to larger, costly Phase 3 trials[18]. Based on the CINAPS criteria, NET-PD investigators selected 4 compounds for further study, of which only one – creatine monohydrate – was not found to be futile, based on a modified futility analysis of 2 clinical trials. As a result, creatine was evaluated in a large, double-blind, randomised controlled, long-term trial (Long-term Study 1 [LS-1] involving 1,741 patients with early PD, in 52 sites across North America[19]. Patients were randomised to receive creatine or placebo and the primary outcome was the difference in clinical decline from baseline to 5 years, using a global statistical test which combined outcomes from a number of motor, non-motor and quality of life assessments. Although the study was designed to run for 5 years, it was terminated early for futility based on a planned interim analysis which detected no difference in clinical outcomes. Subsequently, another international committee of experts was assembled to form the Linked Clinical Trials Initiative (LCT). The aim was to offer a structured approach to identify and prioritise drugs for repurposing in PD to modify disease progression and accelerate into pilot clinical trials [20]. Following an extensive literature review process assessing criteria such as potential modes of action, safety, blood-brain-barrier penetration and preclinical data, 26 candidate dossiers were drawn up. Of those, 7 were chosen to progress into small ‘learning’ clinical trials in PD patients - exenatide, liraglutide, lixisenatide, deferiprone, deferasirox, simvastatin and trehalose.

In parallel with improved methods of identifying potential drugs for repurposing, the development of novel unbiased screening platforms using cell-based assays, small organisms based screening systems and genetically engineered cell lines has helped to generate data required to advance potential candidates into clinical trials[21,22].

This review aims to highlight several repurposed drugs currently in clinical trials being evaluated for their potential disease modifying effects in PD and summarising pre-clinical, epidemiological and clinical evidence for each candidate, with potential further work that needs to be done.

## **2. Drug repurposing in Parkinson’s disease**

### **2.1 Ambroxol**

Mutations in the glucosylceramidase beta acid (GBA1) gene have been identified as the single largest risk factor for the development of idiopathic PD and present in up to 25% PD patients [23]. When present in the homozygous or compound heterozygous state, mutations in this gene cause Gaucher's disease (GD), whereas a single mutation is sufficient to increase the risk of PD. The mechanism underlying the GBA-mediated loss of function in PD are unclear but it is thought to be related to the activity of glucocerebrosidase (GCase), an enzyme encoded by GBA and involved in modulating lysosomal function and folding of  $\alpha$ -synuclein.

Significantly decreased GCase activity is found in the substantia nigra (SN) of GBA-PD patients, but also in patients without GBA mutations [24,25]; while in animal models decreased GCase activity results in increased neocortical accumulation of  $\alpha$ -synuclein and associated cognitive and motor deficits in vivo [26].

Encouragingly these pathological and behavioural abnormalities can be halted by administration of viral gene-therapy mediated overexpression of exogenous GCase [27], though potential issues of distribution to affected tissues has led others to explore the use of utilising small molecules to increase GCase activity. These molecules act as chaperones to increase GCase activity by facilitating the correct folding of mutant GCase molecules in the endoplasmic reticulum to aid their transport to lysosomes [28]. Ambroxol is a secretolytic agent licensed for use in the treatment of respiratory diseases and has been shown to act as a pharmacological chaperone [29] to enhance the activity of GCase in; PD fibroblast lines [30,31]; dopaminergic neurons from patients with PD and GBA1 mutations [32]; *Drosophila* expressing GBA mutations [33]; transgenic mice overexpressing  $\alpha$ -synuclein [34] and non-human primates [35]. Encouragingly, the in vivo data indicated ambroxol could cross the blood-brain-barrier and reduce the levels of  $\alpha$ -synuclein and phosphorylated  $\alpha$ -synuclein [34].

A pilot initial study involving 12 Gaucher disease (GD) patients treated with ambroxol 150mg/day for 6 months demonstrated good safety and tolerability [36]. A second open-label study involved administration of ambroxol in doses ranging from 375mg/day to 1300mg/day to five GD patients for 48 months to assess safety and tolerability [37]. All doses demonstrated increased lymphocyte GCase activity, achieved a mean CSF: serum ratio of 15.6% at the highest doses while improvements in neurological deficits were observed across all patients. These 2 pilot trials in GD have provided tentative support for repurposing ambroxol in PD and 2 trials are currently underway. An open label trial involving 20 patients with PD (both with and without GBA mutations) will primarily evaluate the pharmacokinetics of 1200mg ambroxol daily for 6 months (AiM-PD - NCT02941822). In addition, a 52-week, phase 2 efficacy trial involving 75 patients with Parkinson's disease dementia (PDD) randomised 1:1:1 to either placebo, low dose (525mg daily) or high dose (1050mg daily) ambroxol will evaluate the change in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-

cog) scale (NCT02914366). Despite the relatively quick advance of these molecular chaperones into clinical testing, there still remains uncertainty regarding the mechanism by which GBA mutations increase the risk for PD and influence disease progression. Furthermore, most current chaperones of GCase including ambroxol are in fact enzyme inhibitors, which may complicate potential future clinical development, as their chaperone activity must be balanced against the functional inhibition of the enzyme. Thus novel molecules that do not cross-inhibit other glycosidases or inhibit GCase but still facilitate translocation to the lysosome are in development and may offer better efficacy [38].

## 2.2 Isradipine

The selective vulnerability and degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNpc) in PD is thought to be related to the high energy demands of the spontaneous pacemaking properties of the neurons themselves [39]. This autonomous pacemaking is accompanied by slow oscillations of calcium influx triggered by the opening of plasma membrane Cav1 (Cav1.2, Cav1.3) Ca<sup>2+</sup> channels, which help meet intracellular bioenergetic needs by stimulating mitochondrial intermediary metabolism and oxidative phosphorylation. However with ageing, reliance on these channels increases. This continued generation of free radical species in combination with other stressors that occur in PD such as misfolded  $\alpha$ -synuclein or mutations in GBA1 can lead to increased mitochondrial oxidative stress and subsequent accelerated cell ageing and death [40]. Although the Cav1 Ca<sup>2+</sup> channels participate in pacemaking, they are not essential for the SNc pacemaking function thus antagonizing these channels to limit the source of oxidative stress could potentially attenuate the degeneration of SNc DA neurons. Epidemiological data supports this hypothesis and indicates patients treated with centrally acting dihydropyridine's (DHP's) (calcium channel blockers used for many years to treat hypertension and angina) may have a reduced risk of developing PD [41–43] although this remains controversial [40]. It is thought that of the various subtypes of Cav1 Ca<sup>2+</sup> channels, Cav1.3 channels, rather than the more common Cav1.2 channels are most likely to mediate risk in PD. This is of relevance as most available DHP's preferentially inhibit Cav1.2 channels, however, isradipine, licensed for the treatment of hypertension, has nearly similar affinity for Cav1.2 and Cav1.3 channels in membrane binding assays, and together with good brain bioavailability has made it the most attractive candidate for repurposing [44–46]. Subsequently isradipine has been shown to protect dopaminergic neurons from MPTP- and 6-OHDA-induced toxicity in a dose-

dependent manner, by reverting dopaminergic neurons to a latent juvenile pacemaking mechanism independent of calcium [39,47].

In view of the encouraging data, an initial open-label, dose escalation study of isradipine controlled-release (5-20mg/day) was conducted in 31 patients with early PD to assess safety (STEADY-PD) and demonstrated acceptable tolerability at doses of 10 mg/day or less with leg oedema and dizziness causing intolerance at higher doses[48]. Subsequently the STEADY-PD-II trial, a randomised, double blind, parallel group trial was undertaken in 99 subjects with early PD not requiring dopaminergic therapy to primarily assess a tolerable dosage of isradipine (at 5mg, 10mg and 20mg doses) with secondary outcomes to detect any preliminary efficacy between the different doses after 52 weeks [49]. The primary outcome again confirmed tolerability was dose dependent - 10mg isradipine being the highest tolerated dose. Though there was no overall effect on blood pressure the most common adverse effect was peripheral oedema which occurred in 34% of patients at the 10mg dose. Though not powered for efficacy, data suggested a very modest advantage (~1 point in the total UPDRS score) in patients treated with 10mg isradipine for 12 months [49]. A larger placebo-controlled phase III trial to assess the efficacy of isradipine 10mg daily to slow progression of PD disability is currently underway – STEADY-PD-III (NCT02168842) with results expected in 2019. The trial involves 336 early PD patients initially not requiring dopaminergic therapy with the primary outcome designated as the change in total UPDRS score in the on-medication state. While the results are eagerly anticipated, a number of potential limitations await. While the design will allow for determination of any long term benefits of isradipine on motor complications and long term PD medication use, if any potential advantages over placebo are detected, it may be difficult to exclude unexpected symptomatic effects (though these were minimal in the previous clinical trial). Furthermore, isradipine has been shown to have dose dependent neuroprotective effects in animal models, with higher doses conferring better protection and it unclear whether the 10mg/day isradipine dose will be sufficient in the current clinical trial. Emerging candidates from pre-clinical studies including novel, highly selective Cav1.3 antagonists may offer more promising results in the future without producing adverse effects that accompany general antagonism of L-type calcium channels [50].

### **2.3 Inosine**



Growing data from prospective studies [51–54] and Mendelian randomisation studies [55,56] indicate a decreased risk of developing PD in individuals with elevated levels of serum urate, an antioxidant, though the association appears weaker and less consistent in women [57–60]. Furthermore, elevated urate levels in serum and CSF from PD patients are associated with a reduced rate of disease progression [61]. In addition, pre-treatment of rodents to elevate urate levels conferred protection against dopaminergic cell death induced by MPTP, 6-OHDA, and rotenone in toxin based models of PD. These effects were thought to occur via modulation of Akt-GSK-3B signalling and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein - a master regulator of the oxidative stress response [62–64].

In view of the data supporting a neuroprotective role for urate in the disease pathogenesis of PD, clinical studies have been undertaken to evaluate the effects of manipulating urate levels using its precursor inosine, a freely available dietary supplement taken by athletes to improve aerobic performance. The SURE-PD trial, a randomized, double-blind, placebo-controlled, dose-ranging trial of inosine enrolled 75 patients with early PD not yet requiring any medication and randomised them 1:1:1 to receive either placebo, inosine titrated to produce mild serum urate elevation (6.1-7.0 mg/dL), or moderate urate elevation (7.1-8.0 mg/dL), for 25 months, with the primary end point being safety, tolerability, and ability to raise urate levels in serum and CSF [65]. Inosine was well tolerated though 3 patients developed symptomatic nephrolithiasis. It was associated with a favourable rate of progression based on changes in UPDRS scores over 24 months which after adjustment for baseline differences, amounted to ~1 point per year on the total UPDRS scale. Although the trial data was not powered to determine efficacy, there was no difference between the time to require dopaminergic therapy between groups, and few patients reached the 2-year analysis time point. Furthermore, elevated serum urate has also been shown to increase the risk of hypertension, coronary heart disease, gout and stroke over the longer term. Although the number of PD patients so far treated with inosine is small, these side effects are potentially problematic for older patients with PD, potentially limiting its utility [66], though a recently reported trial of 10 PD patients of Asian origin treated with inosine to elevate urate levels to 6.0-8.0mg/dL reported no adverse effects after 1 year of treatment [67]. A multi-centre, randomized, double-blind, placebo-controlled trial, SURE-PD3 (NCT02642393) is currently underway to evaluate the effects of elevating serum urate to 7.1-8.0 mg/dL using inosine in early PD patients. The trial involves 240 patients and the primary outcome is the rate of clinical decline as assessed by the change in MDS-UPDRS Part 3 over 24 months with results expected in 2020.

## 2.4 Ursodeoxycholic acid (UDCA)

Given the importance of mitochondrial function in the pathogenesis of sporadic and familial Parkinson's disease [68], researchers screened 2000 compounds from the Microsource Compound library to assess their rescue effects on mitochondrial function in parkin (PARK2) mutant fibroblasts in a novel high throughput assay to identify potential compounds for repurposing in PD [21]. Two compounds were identified - ursocholic acid and the related compound dehydro-ursolic acid lactone (11,12). As neither were licensed drugs with little clinical safety data available, researchers then evaluated the effects of the closely related ursodeoxycholic acid (UDCA). UDCA has been used as treatment for cholestatic liver disease for a number of years and is a first line treatment for primary biliary cirrhosis. UDCA was subsequently shown to rescue mitochondrial function in both parkin and LRRK2 mutant fibroblasts, possible via increased phosphorylation of Akt. UDCA has also demonstrated potent anti-apoptotic, anti-oxidant and anti-inflammatory effects in hepatocellular models [69,70] and has demonstrated that these effects extend to several neurodegenerative models of disease including PD. UDCA has been shown to be able to partially rescue a PD model of *C.elegans*, increase survival of nigral transplanted tissue in rodents resulting in improved behavioural function [71,72], and attenuate dopaminergic cell loss in vivo induced by rotenone [73]. These findings were thought to be related to beneficial effects on mitochondrial and inflammatory pathways and regulation of the PI3K-Akt pathway[74].

In regards to potential repurposing for PD, data from a clinical trial of UDCA in 18 patients with amyotrophic lateral sclerosis (ALS) treated for 4 weeks at doses ranging from 15mg/kg/day to 50mg/kg/day indicated a CSF: serum ratio of approximately 0.6% at the highest 50mg/kg/day dose [75]. Although the trial reported good tolerability the current licensed dose of UDCA is 10-15mg/kg/day, with an increased risk of hepatocellular carcinoma and liver toxicity reported at doses of 28mg/kg/day and so further long term PD-specific data regarding safety, tolerability and CSF studies are needed [76]. A phase 1, open-label trial evaluating the safety and pharmacokinetics of 50mg/kg/day UDCA in 20 patients with PD is currently underway (NCT02967250) while a trial of UDCA in PD patients to evaluate the effect of on disease progression has received funding and is due to start imminently. PD-specific pharmacokinetic data regarding UDCA is awaited though in view of the potential issues regarding incomplete absorption of UDCA from the gut, interest is growing in the UDCA derivative tauro-ursodeoxycholic acid (TUDCA) (not currently approved for use), which has demonstrated better orally bioavailability, crosses the blood-brain barrier and has demonstrated neuroprotection against MPTP- and  $\alpha$ -synuclein-induced stress in vitro and in vivo [72,77–79] and indicated potential benefits in a small RCT in 34 patients with ALS [80] and may offer better potential.

## 2.5 Deferiprone

Growing evidence suggests dysregulation of cerebral iron homeostasis occurs in several neurodegenerative disorders including PD and thus represents a novel therapeutic target. Although iron accumulates in the brain as part of normal ageing, increased regional iron accumulation has been observed in the SN in patients with sporadic PD in post-mortem, MRI and transcranial ultrasonography imaging studies [81–83], while some studies suggest the degree of nigral iron deposition may relate to motor severity [84]. Further studies have confirmed excess iron deposits in individual dopaminergic neurons in the SNpc are associated with neuromelanin granules, Lewy bodies and activated microglia [85–87]. This excess labile iron can influence neurodegeneration by generating reactive oxygen species, activating microglia and pro-inflammatory pathways, promoting  $\alpha$ -synuclein misfolding and aggregation and triggering cell death by iron-dependent pathways termed “ferroptosis” [88–90] - thus removal of excess cerebral iron in PD may be a useful strategy [91]. Current studies regarding iron chelation in PD have focused on deferiprone, licensed as a treatment for thalassemia syndromes and cardiac iron-overload diseases at doses of 75 to 100 mg/kg/day. Unlike other iron chelators, deferiprone can redistribute excess intracellular iron to the extracellular apotransferrin to avoid severe systemic iron losses and can cross the blood-brain-barrier in rodent models[92]. Furthermore, deferiprone has been shown to remove excess labile iron and to attenuate dopaminergic neuronal loss in MPTP mouse models [93]; and inhibit dopaminergic neuron necrosis, ferric ion accumulation and microglial proliferation and reduce the hyperechogenic area of the SN in 6-OHDA rodent models [94,95]. While in a transgenic mouse model overexpressing A53T, deferiprone significantly improved impairments in the rotarod task and the novel object recognition test (though this was not accompanied by changes in  $\alpha$ -synuclein aggregation)[96].

There have been 3 clinical trials of deferiprone in PD. An initial pilot double-blind, randomised-controlled trial (FAIRPARK) with a delayed start design evaluated 40 early stage PD patients randomly assigned to receive oral deferiprone (30mg/kg/day) or placebo for 12 months using the change in iron overload in the SN (as measured by the T2\* MRI sequences) as the primary outcome [93]. The results indicated a 12-month course of deferiprone significantly reduced foci of accumulated iron in the SN of PD patients without detectable changes in other brain areas or systemic levels. In addition, the early start (deferiprone treated) group showed a reduction in the UPDRS motor subscale in the early start group (-2.3 +/- 0.6) compared to the delayed start group (+1.0 +/- 0.7) which was sustained at 12 months – though improvements waned after 18 months continuous treatment

[93]. Further post hoc analysis indicated PD patients with lower caeruloplasmin ferroxidase activity appeared to respond better to chelation therapy [97]. In a recently completed phase 2 double blind placebo controlled study (Deferiprone PD), 22 patients with early stage PD were randomized to receive deferiprone 20 or 30 mg/kg/day or placebo for a period of 6 months with the primary outcome being changes in regional brain mineralization as assessed with T2\* MRI [98]. Deferiprone treatment led to reduced dentate and caudate nucleus iron content compared to placebo with three patients showing alterations in the T2\* MRI values for SNc. In addition, patients receiving the 30 mg/kg dose of deferiprone showed a non-statically significant trend for improvement in motor-UPDRS scores and quality of life. Deferiprone was generally well tolerated though 5 patients across both studies developed neutropenia necessitating early drug withdrawal.

These studies have provided support for the repurposing of deferiprone in PD though further questions remain regarding the iron chelator of choice. Although deferiprone has been used in the majority of neurodegenerative trials, deferrioxamine has been similarly shown to reduce excess brain iron deposits in patients with aceruloplasminemia [99] and prevented aggregation of  $\alpha$ -synuclein reduced oxidative stress in dopaminergic neurons, though it is unable to cross the blood brain barrier [100]. This may suggest the ability to cross the blood-brain-barrier may not be necessary for brain iron removal and that these two agents have different pools of chelation – potentially indicating combination therapy (which has proved efficacious in the treatment of other iron storage disorders) may be more beneficial [101]. Nevertheless, whether excessive iron represents a cause or consequence of dopaminergic neuronal cell death is uncertain however the short-term efficacy results are highly encouraging. While it remains to be seen whether observed clinical benefits in PD patients occurred as a result of iron chelation alone or via permissive effects of chelation on dopaminergic treatments, other preliminary successes of iron chelation in neurodegenerative disease such as Friedreich's Ataxia [102] provide further support to its potential and further phase II/III trials are now underway. A randomised, double-blind, placebo-controlled trial is underway involving 338 patients with treatment naïve PD patients evaluating the use of deferiprone 30mg/kg/day on the total MDS-UPDRS score at 36 weeks (FAIRPARK-II, NCT02655315); and a randomised, double blind trial of deferiprone in 140 patients with PD assessing doses of deferiprone of 600 to 2400mg/day on the MDS-UPDRS Part 3 over 9 months (SKY, NCT02728843).

## **2.6 Exenatide**

A meta-analysis of longitudinal cohort studies has identified Type 2 diabetes (T2DM) as a modest risk factor for developing PD (RR 1.32)[103,104] though the heterogeneity of studies has made it difficult to draw firm conclusions. However, the presence of co-existing T2DM seems to influence disease progression, as patients with co-existing T2DM develop earlier cognitive impairment, gait and balance issues than PD patients without T2DM, even after excluding those with diabetes-related complications such as peripheral neuropathy and vascular complications[105,106]. One hypothesis linking PD and T2DM is disruption of physiological insulin signalling. Neurons are especially vulnerable to stress in the presence of dysfunctional insulin signaling [107], while conversely disrupted insulin signaling leads to accumulation of oxidative stress and PD pathology [108,109], thus linking PD and insulin signaling in a complicated positive feedback system [110]. Indeed evidence of disrupted insulin signalling or “brain insulin resistance” has been demonstrated in post mortem tissue from patients with PD without coexisting peripheral insulin resistance or T2DM [111,112]. Whether these changes are related to the causes of, or are simply consequences of neurodegeneration is unclear, however, there are now considerable data relating central insulin resistance to neuronal survival pathways[113]. Rather than simply administering exogenous insulin to restore these dysfunctional pathways (which comes with inherent risks of administering insulin to non-diabetics) an indirect route to address this aspect of PD pathology is to explore compounds that influence insulin release.

Exenatide is a synthetic glucagon-like peptide-1 (GLP-1) agonist licensed for the treatment of type 2 diabetes as an agent that promotes insulin secretion [114]. Neurotrophic properties of GLP-1 receptor agonists were first identified in 2002 [115] and since that time there have been multiple reports of beneficial effects of GLP-1 receptor agonists in a wide range of toxin-based models of PD including the MPTP, 6-OHDA and LPS models [116][117], as well as 2 alpha synuclein animal models [118] which have allowed investigations into the potential mechanisms of action of GLP-1 agonists, which appear to have multiple effects relevant to the neurodegenerative processes of PD. GLP-1 receptor stimulation has been shown to exert anti-inflammatory effects in some laboratories[116], most convincingly associated with prevention of microglial-mediated conversion of astrocytes to an A1 neurotoxic phenotype [118], which was associated with protection against loss of dopaminergic neurons and behavioral deficits in the  $\alpha$ -synuclein preformed fibril ( $\alpha$ -syn PFF) mouse model of PD. However others have indicated these anti-inflammatory properties may not be necessarily relevant to all of their therapeutic effects[119]. Furthermore neuroprotective and neurorestorative effects have been seen in association with beneficial effects on mitochondrial function[120], synaptic plasticity [115,121], stimulation of neurogenesis [122]as well as through enhancing the actions of BDNF[123]. It is likely that all of these actions

are inter-related possibly through an effect of GLP-1 receptor stimulation on insulin resistance and downstream Akt signaling [124]

There have been 2 trials of exenatide in patients with PD. The first was a small, parallel-arm, open label involving 44 patients with moderate stage PD randomised to receive 10ug exenatide twice daily (Byetta) for 12 months or act as controls. Patients were approximately 60 years old, had a mean duration of PD of about 10 years and were using a mean of 975mg of L-dopa equivalent. The primary outcome was the change from baseline in MDS-UPDRS Part 3 at 14 months (2 months after exenatide withdrawal) measured in the off-medication state after an overnight withdrawal from PD medication with an evaluation performed via video by assessors blinded to treatment allocation. The group randomized to exenatide twice-daily had a 1.7-point improvement at the 14-month point, while the group maintained on conventional medication alone, had deteriorated by 2.8 points by this same point. In addition, among the secondary outcomes, patients on exenatide had improved by 2.8 points on the Mattis dementia rating scale at the 14-month timepoint, while the control group had deteriorated by 3.5 points [125]. After extended follow up in the absence of any further treatment with exenatide, at the 2-year follow up point, exenatide treated patients maintained an advantage of 5.6 points and 5.3 points over the control group on the MDS UPDRS part 3 and Mattis-DRS2 respectively [126]. The drug was well-tolerated in this patient group though the well-known side effects of weight loss, nausea and dysgeusia were more common in the exenatide group and contributed to the early withdrawal of exenatide in 2 patients. Although encouraging, the open-label nature of the trial meant that these results may have been influenced by long-lasting placebo effects and could not be taken as proof of efficacy. Subsequently a double-blind placebo-controlled trial involving 60 patients was performed and recently reported [127]. In comparison to the previous trial, these patients had shorter disease duration (mean 6.4 years) and were on approximately 800mg levodopa equivalents. Patients were randomly assigned to 2mg exenatide once-weekly - Bydureon (chosen due to its lower adverse-effect profile in comparison to the twice-daily formulation) or placebo for 48 weeks after which there was a 12-week washout period before comparing scores on the MDS UPDRS part 3 (assessed again in the off medication state). The exenatide treated group had a statistically significant advantage over placebo of 4.3 points (95%CI -7.1 to -1.6; p=0.0026) and 3.5 points (95%CI -6.7 to -0.3; p=0.0318) at 48- and 60-weeks respectively. There were no other statistically significant differences between the 2 groups on other outcome measures although a post hoc analysis indicated potential beneficial effects on mood/depression in the exenatide group [128] and the direction of effect favored exenatide for almost all measures.

These results, while encouraging, still have to be interpreted with caution and should be regarded as “proof of concept” rather than efficacy. Both trials were small, single-centre studies and therefore despite randomization there were differences in the baseline severity of the patients between the exenatide and placebo groups. Also, although well tolerated and safe in normoglycaemic individuals, a recognised side effect of exenatide and other GLP-1 agonists is weight loss, which can have detrimental effects in patients with advanced PD. Furthermore, despite the existing laboratory data, it has to be convincingly demonstrated in people with PD whether any clinical effects relate to symptomatic effects on the dopamine system or disease-modifying actions on the underlying pathophysiological processes of PD. Careful consideration must be given to trial design to enable clarification of these possibilities[4] and a larger, multi-centre Phase 3 study is due to start soon.

Although exenatide was the first in class of GLP-1 R agonists, there have since been four other GLP-1 agonists licensed for the treatment of T2DM. Lixisenatide (an incretin mimetic like exenatide, based on the structure of exendin-4) and liraglutide, dulaglutide and albiglutide (based on the structure of human GLP-1 and termed GLP-1 analogues). In PD models, data exists for liraglutide and lixisenatide which have similarly demonstrated neuroprotective effects in animal-toxin models of PD, preventing MPTP-, 6-OHDA- and rotenone-induced dopaminergic cell loss and motor impairments which were associated with reduction in pro-apoptotic signalling, pro-inflammatory cytokine production and promotion of neurotrophic factors such as GDNF [129–132].

Although no clinical data from PD patients is available for other GLP-1 agonists, data from a double-blind, RCT assessing the effects of liraglutide on cerebral amyloid deposits in AD patients (which have similar links with dysfunctional insulin signalling) have been reported. This study indicated liraglutide treatment halted decline of cerebral glucose metabolism compared with controls – suggesting an ability to stabilise energy metabolism in areas of the brain that have been shown to correlate with cognitive decline in patients with AD [133]. In addition, data from diabetes trials suggest varying efficacy, tolerability and pharmacokinetics between agents within the class of GLP-1 agonists [134], and thus it is reasonable to assume similar varying efficacy in models of neurodegeneration. There are few studies comparing the relative neuroprotective effects of GLP-1 agonists though one study suggested greater efficacy of liraglutide in comparison to exenatide in an MPTP model of PD (though differences in dosing regimens were not addressed) [132]. Clinical data similarly suggests varying degrees of CNS penetrance between exenatide and liraglutide [127,135] though the relevance of this is uncertain. In summary there is preliminary evidence that GLP-1 agonists may represent a potential new treatment for PD, with encouraging in vitro and in vivo studies hinting at possible mechanisms of action though questions remain regarding the nature of effects seen, dosing, tolerability and long-term outcomes. Reflecting

the promise of this class of drugs in PD, several clinical trials of GLP-1 agonists are underway. A small open-label imaging study involving 20 patients receiving 2mg exenatide once-weekly for 12 months will evaluate any imaging changes utilising functional MRI (NCT03456687); a single centre, double-blind, placebo-controlled efficacy study involving 57 patients with early stage PD will evaluate the effects of liraglutide (1.2 or 1.8 mg) over 14 months on MDS-UPDRS Part 3, Non-motor symptom scale and Mattis Dementia Rating Scale (MADRS-2) scores (NCT02953665); and a multicentre, randomized, placebo-controlled, double-blind phase II trial evaluating the effects of 12 months treatment of lixisenatide 20 µg/day in 158 early stage PD patients, assessing changes in the MDS-UPDRS Part 3 scores (NCT03439943).

## **2.7 Nilotinib**

Nilotinib is a second generation brain penetrant Abelson (c-Abl) tyrosine kinase inhibitor that is licensed for the treatment of Chronic Myeloid Leukaemia (CML) in doses ranging from 300mg-1200mg/day. Accumulating evidence from animal and genome-based studies suggest c-Abl activation plays a role in the pathogenesis of PD and other synucleinopathies. Elevated levels of activated (phosphorylated) c-Abl are found in the SN in post mortem studies of PD patients [136,137] while activation of c-Abl in mice induces neurodegeneration in the hippocampal and striatal brain areas [138]. Further work has demonstrated that c-Abl phosphorylation occurs as a result of mitochondrial dysfunction and oxidative stress [139], can promote accumulation of  $\alpha$ -synuclein through effects on autophagy mechanisms [138] and can promote phosphorylation of parkin, causing inhibition of its ubiquitin E3 ligase activity inducing mitochondrial dysfunction and dopaminergic neuronal death [140]. Taken together, there is ample evidence that c-Abl may be a promising therapeutic target in PD. Due to the relatively better CNS penetration of nilotinib over other c-Abl inhibitors this has garnered the most data in PD studies. Indeed in pre-clinical models of PD, nilotinib has been shown to cross the blood-brain-barrier and reduce c-Abl activity, ameliorating autophagic clearance of  $\alpha$ -synuclein in transgenic and lentiviral gene transfer models [138]. Importantly for potential drug repurposing, these effects were seen at doses far lower (1-10mg/kg/day) than used to treat CML. Furthermore nilotinib prevented dopaminergic cell loss and motor impairments induced by MPTP in mice which were associated with inhibition of parkin phosphorylation, and reduced accumulation of parkin substrate PARIS, thus hinting at another potential mechanism of action [141,142]. Based on these pre-clinical data, a small, open-label proof of concept study was recently conducted to evaluate the safety and tolerability of nilotinib in 12 patients with PD dementia or Dementia with Lewy



bodies followed up for 24 weeks, followed by a final assessment at 12 weeks later [143]. Although neuroprotective effects were seen at low doses of nilotinib in animal models of PD, the choice of dose for the clinical study was necessitated by the lowest doses commercially available of 150mg – 300mg. The authors report nilotinib was well tolerated though one patient in 300 mg dose group was diagnosed with myocardial infarction and two had transient QTc prolongations. There was also evidence of CNS penetration with a CSF: plasma ratio of Nilotinib of 12% and 15% with 300mg and 150mg respectively. Exploratory analysis of clinical outcomes revealed an improvement of 3.4 points and 3.6 points in the 150mg and 300mg groups at 24 weeks, which reverted to baseline at the 36 week follow up. Due to the numerous methodological limitations of the study, interpretation of the findings must be guarded [144]. Although the authors commented that the one patient who suffered a serious cardiac adverse event should be interpreted as a failed screening procedure, known side effects of nilotinib at doses used to treat CML include cardiac conduction abnormalities and sudden cardiac events due to unwanted off-target non-selective tyrosine kinase inhibition and so claims of tolerability should be interpreted with caution. Also given the lack of a placebo control and blinding of the assessors, combined with the known magnitude of placebo effects that can be observed over time periods similar to the study, it is impossible to conclude any effects on efficacy. In addition, despite the changes in dopamine metabolites and markers of neuronal damage the authors report in the CSF, none of the markers used are validated as biomarkers in PD and can vary greatly between patients and track poorly with disease stage and progression. Questions remain in regards to selecting the optimum dose of nilotinib, its brain penetrance, assessments of cardiovascular toxicity and evaluation of unwanted off target effects, however the pre-clinical data and preliminary clinical study results have opened up a new molecular pathway previously untargeted in clinical trials and should be explored further. As a result, two fully randomised, double-blind, placebo-controlled trials are underway. NILO-PD (NCT03205488) will assess the safety and tolerability of daily oral administration of nilotinib (150-300mg/day) for 12 months in 135 PD patients while PD-Nilotinib (NCT02954978) will involve 75 PD patients assigned either to placebo, 150mg or 300mg nilotinib for 12 months to further evaluate safety and tolerability and explore efficacy. Emerging research into more potent, selective c-Abl inhibitors is already showing promise in preclinical models of PD [145].

## **2.8 Simvastatin**

Statins, as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) are widely prescribed for their effects on lowering cholesterol and reducing cardiovascular risk. Studies have shown statins can also modulate a number of biological processes known to be relevant to the pathogenesis of neurodegenerative diseases including PD, including attenuation of  $\alpha$ -synuclein aggregation, inhibition of oxidative stress and pro-inflammatory pathways, stimulation of nitric oxide synthase and promotion of neurotrophic factors [146,147].

Pre-treatment with simvastatin preserved dopaminergic cells and motor behaviour in rodents treated with 6-OHDA, possibly via activation of the NADPH oxidase/p38 MAPK pathway promoting antioxidant protein expression or via modulation of NMDA receptor and pro-inflammatory cytokine expression [148–150].

Similarly in MPTP models, at doses equivalent to those licensed in humans, pre-treatment with simvastatin suppressed activation of NF- $\kappa$ B, protected dopaminergic neurons and improved motor function [151,152].

Unfortunately, despite encouraging pre-clinical studies, epidemiological data regarding the association between statin use and the risk of PD is unclear, confounded by the use of statins themselves and their relationship to cholesterol, meaning studies have suggested statins are associated with an increased risk, decreased risk or no risk. The most recent meta-analysis concluded a modest protective effect of statins that disappears when adjusted for cholesterol level [153]. However, based on its promising biochemical, pharmacological safety & efficacy profile [20], and ability to cross the blood-brain-barrier, simvastatin 80mg daily is currently being evaluated in a phase 2 double-blind, randomised controlled, multicentre trial involving 235 patients with moderate stage PD (Hoehn&Yahr <3.0). Patients will be followed by for 24 months, with a final assessment at 26 months after drug withdrawal with the primary outcome specified as the change in MDS-UPDRS part III (OFF) score.

### **3. Conclusion**

As well as the drugs discussed here, there are numerous other candidates being assessed for potential repurposing in PD with preliminary human trials in planning (Table 1). Despite the potential advantages drug repurposing offers, as a strategy it offers unique challenges including the unavoidable need for expensive and risky clinical trials to demonstrate safety and efficacy in a new population while the limited patent protection often means a lack of commercial interest or incentive for further investment [149]. In addition, as the failed clinical trials of repurposed drugs pioglitazone, creatine, co-enzyme Q10 in PD have shown, despite promising

pre-clinical evidence, repurposing available drugs for PD is not guaranteed for success. It is outside the scope of this article to explore the various aspects of why these trials failed, but this likely relates to our still limited understanding of PD pathogenic mechanisms; inadequate animal models to in which to screen interventions which re-capitulate human PD; the heterogeneity of PD and the lack of any biomarkers with which to monitor disease progression and response to treatment (see [154] for review). Furthermore, given the clinical and pathological heterogeneity of PD, it is unclear whether utilising cohorts with genetic abnormalities and directing treatments at correcting those defects as per the ambroxol trials or using a broader approach to detect changes in heterogeneous population will prove fruitful. Still further questions remain regarding the “single-target” approach. As PD has multifactorial aetiologies, it might be more appropriate to offer combinations of compounds that target different but potentially complementary biological mechanisms. Also, as the above examples attest, many of the current drugs in clinical testing have various “dirty” off-target or unintended adverse effects that may limit their maximal therapeutic potential. Even if these trials fail to report positive outcomes, they may indicate a signal of effect that may potentially be optimised by molecules specifically designed to engage similar targets with improved brain penetration / ligand binding / selectivity [155].

Despite these challenges, the appropriate use of drug repurposing remains an appealing method for accelerating much needed treatments in PD, offering established safety data and substantially reducing the costs of clinical development. In addition, advances in computational models and novel high-throughput screening have identified numerous potential candidates for potential use in PD while in parallel new funding opportunities for small pilot learning trials has allowed increased opportunity for collaboration between academia and the pharmaceutical industry and we are cautiously optimistic that a therapy that can alter the course of disease progression in PD may be on the horizon.

### **Compliance with Ethical Standards**

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#### **Potential conflicts of interests**

DA has no conflicts of interest. TF has received honoraria from Profile Pharma, BIAL, AbbVie, Genus, Medtronic, and St Jude Medical. DA and TF are investigators on the Exenatide-PD trial.



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Table 1: Emerging candidates for repurposing for the treatment of Parkinson's disease

Drug name / class	Original intended / licensed use	Proposed mechanism of action	Epidemiological / pre-clinical evidence
$\beta$ 2-selective adrenoceptor ( $\beta$ 2AR) agonists	Respiratory diseases	Reduces SNCA expression, inhibitor of microglia activation	Patients prescribed salbutamol associated with reduced incidence of PD (RR 0.66; 95%CI 0.58–0.76); patients treated with propranolol (n = 14,794), a B2AR antagonist, had increased incidence of PD (RR 2.20; 95%CI 1.62–3.00) [156] Reduced SNCA gene expression in human neuroblastoma cell lines and in SN in wild-type mice [156] Prevented nigral neuronal loss in a MPTP mouse model [156] and 6-OHDA model via inhibitory effects on microglia [157]
MSDC-0160	Originally formulated for Type 2 diabetes	Targets mitochondrial pyruvate carrier (MPC) modulating cellular function	Preserved cerebral 2-deoxyglucose uptake after 3 months of use in AD patients [158] Attenuates neurodegeneration in MPTP model, $\alpha$ -synuclein-based <i>C. elegans</i> model and cultured human midbrain dopamine neurons [159].
EPI-589 (Troloxamide quinone)	Childhood mitochondrial disease	Anti-oxidant NAD(P)H dehydrogenase (quinone) modulator	No published pre-clinical data. Open-label Phase 2A study involving 40 (PINK1, parkin or LRRK2) PD patients ongoing to evaluate safety and biochemical changes after 3 months treatment (NCT02462603).
N-acetyl-cysteine (NAC)	Cystic fibrosis, acetaminophen toxicity	Antioxidant Anti-inflammatory Neurotrophic	Oral NAC prevention of DA cell death and motor abnormalities in MPTP and transgenic mice overexpressing $\alpha$ -synuclein and hESC-derived midbrain dopamine (mDA) neurons treated with rotenone [160–162] IV NAC raised brain glutathione levels in PD patients [163] not replicated by oral administration [164]

