Clinical Trial Highlight

Clinical Trial Highlights: Modulators of Mitochondrial Function

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Mitochondria are involved in many dynamic processes, including their role in the production of the cell's energy currency, adenosine triphosphate (ATP). This production is carried out through a complex chain of chemical reactions, followed by the transition of electrons through four protein clusters on the mitochondrial membrane called respiratory complexes. This transfer drives protons across the membrane creating a high concentration on one side of the membrane. The difference in concentration, known as the mitochondrial membrane potential (MMP), allows the flow of protons through respiratory Complex V to combine adenosine diphosphate with phosphate to create ATP [1].

Mitochondrial problems were first discovered in Parkinson's Disease (PD) in the 1980's when drug users injected contaminated heroin and subsequently developed parkinsonian symptoms [2]. Further investigation in animal models identified that the contaminant was 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which was metabolised to 1-methyl-4-phenylpyridinium (MPP+),an inhibitor of mitochondrial respiration [2, 3]. Inhibition of mitochondrial respiration with MPP+results in reduced ATP levels and the production of harmful reactive oxygen species [4–6]. Mitochondrial dysfunction in PD was later confirmed when reduced

respiratory complex activity was identified in post-mortem substantia nigra samples from PD patients [7]. Following this discovery mitochondria became the focus of intense research in PD.

As genetic screening became more prevalent, several mutations in mitochondrial related genes were discovered to be associated with increased risk of PD, these genetic variants include *PINK1* [8], *Parkin* and *DJ-1* [9]. While other genetic variants have been associated with a functional decline in the mitochondria but don't have a direct mitochondrial link, for example *LRRK2* [10–12], *VPS35* [13] and *SNCA* [14]. The study of these genetic variants has shaped our understanding of mitochondrial involvement in PD. Parkin and PINK1 proteins are both vital to the clearance of defective mitochondria. Work in animal models and patient tissue suggests that Parkin and PINK1 mutants have reduced respiratory complex I activity, low levels of mitochondrial respiration and morphological changes in the mitochondria [15–21]. Parkin models have also shown reduced MMP and ATP levels [15]. A vast amount of research has also assessed mitochondrial dysfunction in LRRK2 mutants. Mutant LRRK2 patient-derived fibroblasts and induced dopaminergic neurons display reduced mitochondrial functioning, ATP levels and respiratory complex activity [10, 11, 22–25]. However, they show a reduced activity in complex III and IV, unlike other forms of PD [10]. Interestingly it is suggested that LRRK2 mutations slow the clearance of defective mitochondria leading to a dysfunctional network [26]. There are conflicting reports about mitochon-

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drial morphology in LRRK2 models, although this may be due to the use of different disease models. Some demonstrate that mitochondria are elongated in both mice models and patient-derived fibroblasts [11, 12], while others report a fragmentation of the network [27, 28]. All this evidence suggests that mitochondrial dysfunction is a crucial component to the pathogenesis of genetic PD.

Research into sporadic PD is far more conflicting leading researchers to theorise that PD is a mechanistically heterogeneous disorder, meaning that different patients have defects in different pathways which are primary drivers of cell death [29]. Evidence suggests that mitochondrial dysfunction is one of these defects and heterogeneity would explain the contradictory reports about mitochondria function in sporadic PD. For example, respiratory complex I activity has been shown to be reduced in patient post-mortem substantia nigra, muscle, and various blood cell types, however, other studies report no deficit in the same tissues [7, 30–32]. Reports of deficits in respiratory complexes II, III and IV are also occasionally observed [30–35]. While studies on other markers of mitochondrial function have reported differences as well, MMP has been observed to be increased [36], decreased [37] or the same [38] as healthy individuals in different studies. Mitochondrial morphology is also altered in sporadic PD patients. Mitochondrial shape and size were found to be variable in post-mortem brain and muscle tissue [39, 40]. Whereas another study showed that mitochondria are swollen and enlarged [37] and a study in 2020 reported a decrease in mitochondrial size and increased fragmentation of the mitochondria [36]. These conflicting results may be driven by the small-scale nature of some of these studies and the complex heterogeneity of sporadic PD.

Several large studies in patient-derived fibroblasts found that there was no difference in mitochondrial activity between controls and patients, this includes respiratory complex activity [41], basal respiration [42] or MMP and ATP levels [38]. Carling et al. (2020) took this one step further and stratified their cohort, identifying a mitochondrial dysfunction subgroup. These patients displayed reduced levels of respiratory complexes as well. This suggests that a proportion of the sporadic PD population are affected by mitochondrial dysfunction and that further classification of PD may be required to personalise patient treatments.

As mitochondria are so pivotal to cellular, and in particular neuronal function, it is clear that any therapeutic which boosts mitochondrial function will be beneficial to PD patients. It should be recognised that mitochondrial dysfunction is unlikely to be the main driving cause of disease in all patients. However, it is theorised that restoring mitochondrial function in patients will slow progression, even if mitochondrial dysfunction is not the direct cause but a secondary mechanism of disease. The enhanced ATP levels and reduced ROS production could reduce cell stress and prolong the life of the cells.

OVERVIEW OF MITOCHONDRIAL MODULATORS IN PD CLINICAL TRIALS

Since the 1980's mitochondrial dysfunction has been recognised in PD [2], yet there are still very few mitochondrial modulators being utilised as prospective disease modifying therapies in PD. There is one compound, Ganoderma, in phase 3 clinical trials and this compound has multiple targets including mitochondria (Tables 1 and 4). Coenzyme Q10, a mitochondrial antioxidant, has been investigated in several phase 2 and 3 trials with mixed results [43–47]. Although all doses were well tolerated and safe, meta-analysis of 8 trials demonstrated that Coenzyme Q10 did not improve motor symptoms [48].

Three compounds are currently considered to be the top mitochondrial modulators, two of these are the repurposed compounds UDCA and terazosin, and the third is a supplement called nicotinamide riboside. UDCA, a drug approved to treat primary biliary cholangitis, was tested in a small pilot study at an increased dose of up to 50 mg/kg over six weeks. 7 Tesla 31Phosphorous-Magnetic Resonance Spectroscopy (31P-MRS) indicated a possible beneficial effect in the three patients who had neuroimaging [49]. Payne and co-workers recently completed the UP study assessing UDCA in 30 patients with recent onset PD. UDCA was safe and extremely well tolerated achieving the trials primary outcome. 31P-MRS confirmed midbrain target engagement and gait analysis suggested a possible beneficial effect on

Table 1
List of active clinical trials

Clinical Trial ID	Compound	Status
NCT05109364	Terazosin	Recruiting
NCT04386317	Terazosin	Recruiting
NCT04152655	Idebenone	Recruiting
NCT05589766	Nicotinamide Riboside	Recruiting
NCT03568968	Nicotinamide Riboside	Recruiting
NCT03594656	Ganoderma	Recruiting

Table 2
List of Terazosin clinical trials.

Clinical Trial ID	NCT03905811	NCT05109364	NCT04386317	NCT05855577
Phase	1	2	2	4
Status	Completed	Recruiting	Recruiting	Not Yet Recruiting
Sponsor	University of Iowa Hospitals and Clinics	Cedars Sinai Medical Center	Cedars Sinai Medical Center	I.R.C.C.S. Fondazione Santa Lucia
Objective	To assess safety and tolerability in pwp	To assess the effect on motor and non-motor symptoms, cardiac changes and brain changes over a long period in patients with pre-motor PD symptoms	To assess the effect on cardiac changes in patients with iRBD	To assess the effect on motor and non-motor symptoms and metabolic variables (breathing, heart rate and blood proteins)
Completion Date	18th November 2020	1st November 2025	30th December 2025	

Table 3
List of Nicotinamide riboside clinical trials

Clinical Trial ID	NCT05589766	NCT05344404	NCT03568968	NCT03816020	NCT04044131
Phase	n/a	n/a	n/a	n/a	2
Status	Recruiting	Completed	Recruiting	Completed	Completed
Sponsor	Haukeland University Hospital Bergen, Vestland, Norway	Haukeland University Hospital Bergen, Vestland, Norway	Haukeland University Hospital Bergen, Vestland, Norway	Haukeland University Hospital Bergen, Vestland, Norway	Istanbul Medipol University Hospital
Objective	A dose optimization trial in PD	Safety of High-dose NR in PD	A randomised controlled Trial of NR supplementation in Early PD	Determine if NR has an impact on the neurometabolic profile in PD patients and if high dose oral NR improves motor symptoms associated in PD	Determine metabolic improvement in AD and PD by dietary supplementation with cofactors N-acetylcysteine, L-carnitine tartrate, nicotinamide riboside and serine
Completion Date	31st December 2024	1st July 2022	15th March 2024	10th February 2020	20th April 2021

Table 4
List of Ganoderma clinical trials

Clinical Trial ID	NCT03594656	NCT00224263
Phase	3	2
Status	Recruiting	Completed
Sponsor	Xuanwu Hospital, Beijing	Xuanwu Hospital, Beijing
Objective	Test the effect of GI on modifying disease progression in untreated PD patients	Test the effect of GI on non-motor symptoms of PD and test its effect on PD progression
Completion Date	31st December 2021	February 2008

motor symptoms. However, there were no significant changes in the clinical assessment based on the UPDRS/part 3 clinical rating scale, but the study was also vastly underpowered to robustly detect a possible difference in UPDRS/part 3 [50]. Terazosin, a drug approved for hypertension and prostate hypertrophy, was also tested in an early proof of concept study in gradually increasing doses up to 5 mg daily. 3 out of 8 patients started on Terazosin dropped out due to orthostatic hypotension or dizziness. However, they reported an interesting correlation between whole blood ATP levels and changes in 31P-MRS in the 5 patients who completed the treatment compared to the 5 patients on placebo [51]. Two ongoing terazosin trials are targeting patients displaying early symptoms of pre-motor PD such as rapid eye movement sleep behaviour disorder (RBD) to try and prevent the development of motor symptoms of PD (Tables 1 and

2). These types of studies may become the future of PD clinical trials as mitochondrial compounds cannot restore neurons but can slow or prevent their degeneration.

Isradipine, a dihydropyridine calcium channel antagonist, that indirectly reduces mitochondrial "burden" has been tested at phase 1, 2 and 3 in PD. Despite early successes the phase 3 clinical trial failed to achieve the primary outcome of improving motor symptom UPDRS scores [52]. This trial may highlight the fundamental issues with PD clinical trials. While isradipine studies were based on solid preclinical data and supported by epidemiological studies, there was no data on target engagement, which is the ability to impact the desired mechanism at the dose tested. Therefore, several additional aspects need to be considered for future trials of isradipine and other compounds. It is suggested that target engagement measures should be included, much like terazosin and UDCA which utilise 31'P-MRS, to confirm doses are adequate to protect neurons. Trials should also aim to add additional outcomes beside the UPDRS score difference, as changes in the UPDRS score are not linear and with each clinical trial the placebo group can change at different rates [53]. Unfortunately, this is difficult without a biomarker of disease, but the use of motion sensors may provide support for upcoming trials.

Multiple supplements have putative mitochondrial beneficial effects. Vitamin D, melatonin and nicotinamide riboside are all commercially available and therefore trials assessing these compounds do not always have a phase allocation. These supplements showed no side effects after administration and have a positive effect on mitochondrial function. However, convincing data on beneficial effect is lacking.

Mitochondrial modulators have become an extensive area of development across many diseases, which means many compounds are undergoing preclinical testing. Two ways of improving mitochondrial function are to remove dysfunctional mitochondria by a process of recycling called mitophagy or by increasing the production of new mitochondria. For example, The Silverstein Foundation is funding research into modulators of Miro1, a key contributor to the transport of mitochondria for recycling. RNS60 by Revalesio and MSDC-0160 by Metabolic Solutions Development upregulate production of new efficient mitochondria. However, many companies are assessing compounds that have a beneficial effect on mitochondria in models of disease but do not have a known or published mechanism of action, such as those from Pretzel Therapeutics and Lucy Therapeutics. This is not an exhaustive summary of preclinical compounds due to the vast range in targets, companies, stages of development and evolving nature of drug development pipelines.

UDCA

Background : There have been 2 clinical trials completed assessing UDCA. One was a small phase 1 clinical trial by the University of Minnesota and the second was a phase 2 trial by the University of Sheffield. 11 papers have been published assessing UDCA's ability to restore function in PD models.

UDCA is a secondary bile acid that is produced by bacterial metabolism in the gut, where it is partially absorbed into the bloodstream. Endogenously UDCA accounts for ∼5% of bile acids in humans.

A drug screen targeting mitochondrial dysfunction in Parkin mutant patient-derived fibroblasts identified that UDCA and similar bile acids rescued ATP and MMP levels [54]. Further studies in LRRK2 G2019 S patient fibroblasts found it rescued ATP levels [10] and in sPD patients it improved Complex I and IV activity as well as MMP and ATP levels [38]. Interestingly, a subsequent study observed lower levels of UDCA in PD patients developing mild cognitive impairment than normal cognition patients, suggesting UDCA may play a role in progression [55]. UDCA was also successful in animal models rescuing ATP and MMP while preventing neuronal death from toxin insult by rotenone and MPP+, known mitochondrial toxins that induce parkinsonism [56, 57]. UDCA, which is already licensed to treat primary biliary cholangitis, has been shown to be well tolerated and safe in patients with motor neuron disease, while also being brain penetrant [58]. Therefore, this repurposing study was able to bypass phase 1 and start a phase 2 trial.

The "UP" study was a proof-of-concept study, meaning it aimed to assess safety, target engagement and efficacy but does not have the participant numbers to reliably assess efficacy. It enrolled 31 patients across two centres. Participants took 30 mg/kg daily and were assessed over 48 weeks with an 8-week washout period following week 48. This trial utilised 31'P-MRS to assess ATP levels in the putamen and striatum in order to understand target engagement. It also assessed participants with OptoGait and Opals systems, which are motion sensors that enable a quantification of movement and walking, to enable the unbiased, quantified assessment of motor symptoms [59].

Title : Trial of Ursodeoxycholic Acid (UDCA) for Parkinson's Disease: The "UP" Study

Phase : 2

Status : Completed

Clinical Trial ID : NCT03840005

Sponsor : Sheffield Teaching Hospitals NHS Foundation Trust

Study design : A randomised double-blind, placebo controlled 48-week trial of UDCA at a daily dose of 30 mg/kg in patients with early Parkinson's disease < 3 years post diagnosis.

Outcome measure : The primary outcomes aimed to assess the safety and tolerability in a Parkinson's population by reporting serious adverse events and the numbers of participants to complete the study.

Secondary outcome measures were assessed as the change from baseline at week 48 in the following:

- MDS-UPDRS scores, in the practically defined 'OFF' state.
- ATP, phosphocreatine and phosphate levels in participant brains, measured using 31P-Magnetic Resonance Spectroscopy.
- Supervised, sensor-based gait analysis.

Comments : The UP study confirmed excellent safety and tolerability of UDCA at a dose of 30 mg/kg. Serious adverse events were only observed in a patient on placebo, the only two treatment-related adverse events with increased frequency in the UDCA treatment group were mild diarrhoea and nausea. Compliance, patients taking the correct tablet regime, was excellent in all patients completing the trial (>97% in the UDCA treatment group). 31P-MRS confirmed midbrain target engagement of UDCA and sensor-based gait analysis suggested a possible beneficial effect of UDCA. In contrast, clinical assessment applying UPDRS/part 3 failed to detect a difference but the study's limited number of participants makes it too underpowered to detect a possible benefit of UDCA on disease progression.

Terazosin

Background : There are 4 clinical trials testing terazosin in PD patients, these are summarised below in Table 2. One is a completed phase 1 clinical trial and the others are trials recruiting patients with pre-motor PD symptoms. 2 papers have been published assessing terazosin's protective effect in PD models.

Terazosin is an α-adrenergic blocker used to treat benign prostatic hyperplasia (enlarged prostate) and hypertension. It also binds to phosphoglycerate kinase 1, the first enzyme in glycolysis [59]. Glycolysis is the first stage of respiration and the production of ATP; it produces pyruvate that is then utilised by mitochondria in respiration.

In vitro and *in vivo* studies found that terazosin increased ATP levels in cells and brain tissue of various PD models, while also preventing neuron loss [60] and protected against cognitive impairment in mouse ventral tegmental area dopamine depleted mice [61]. 4 epidemiological studies have assessed the incidence of PD in populations of patients taking terazosin or tamsulosin, which is also used to treat high blood pressure. These studies observed differing effects of terazosin with some showing it lowered the risk of PD compared to those taking other high blood pressure medication, while one found no difference compared to a control group. However, there is some debate about the selection of an accurate control group and possible effects of undiagnosed PD at initial assessments [60–64].

The two trials by the Cedars Sinai Medical Center are interesting because they are targeting patients that are not displaying PD motor symptoms (Table 1). Their aim is to select participants that are showing early risk signs of PD and treat to prevent/slow the onset of PD by preventing the early loss of neurons.

A newly registered clinical trial by the I.R.C.C.S. Fondazione Santa Lucia is a phase 4 clinical trial assessing terazosin and a supplement, Lisosan-G, in 50 pwp. The main aim of the study is to validate metabolism indicators as possible biomarkers for further studies and to assess the engagement of both compounds in Nrf2 activation. Nrf2 is part of the antioxidant response and therefore has a secondary impact on mitochondrial health when activated [65].

The pilot study by the University of Iowa was the first study to be completed for terazosin in PD. It tested safety and tolerability in 13 pwp. This study did not have enough participants to adequately assess efficacy but aimed to guide the design of future studies and assess terazosin's effectiveness and target engagement to support results from animal model studies. One of the main aims was to assess the frequency of falls for the patients as terazosin lowers blood pressure which is already known to dramatically reduce in pwp when they stand up. This study is outlined in more detail below.

Title : Terazosin and Parkinson's Disease Extension Study

Phase : 1

Status : Completed

Clinical Trial ID : NCT03905811

Sponsor : University of Iowa Hospitals and Clinics

Study design : a single centre, randomised, double-blind, controlled, pilot study to assess the safety and tolerability of terazosin at a dose of 5 mg daily for patients with PD. 8 participants were given terazosin and 5 placebo for a 12 week period.

Outcome measure : The primary outcome measures were to assess the number of participants that report adverse events, falls and drop out.

The secondary outcomes assessed:

- The change in blood pressure at 0, 2, 6 and 12 weeks.
- The number of participants with intolerable side effects.
- The number of participants not complying with the treatment regime.

Comments : As reported in Schultz et al. (2022), 3 out of 8 participants receiving terazosin dropped out due to dizziness and/or drops in blood pressure when standing up. However, 31'P-MRS results showed that terazosin significantly increased the ATP/phosphate ratio in the cerebral cortex compared to the placebo group. Similar increases in ATP were observed in the blood of participants as well. Although one patient did report a decrease in ATP levels which returned towards original levels after a 12 week wash out period of terazosin, this was unexpected and should be monitored in future trials. Although this is a small pilot study it shows that terazosin appears to effectively engage its target in pwp, but future studies should closely monitor the blood pressure of participants due to safety concerns.

Idebenone

Background : There is one trial currently for idebenone and it is a large-scale trial targeting pre-motor symptom PD patients aiming to prevent/slow progression of the disease before too many neurons are lost (Table 1). Similar to one of the pre-motor symptom terazosin trials, it selected participants that manifest RBD, a common early non-motor symptom of PD.

More than 100 papers have been published on idebenone, which has been used for treating different types of diseases such as Leber's hereditary optic neuropathy [66], Duchenne muscular dystrophy [67], Friedreich's ataxia [68] etc, but at the moment very few (4 papers) have been published regarding the use of idebenone for treating PD.

Idebenone is a short-chain benzoquinone, an analogue of coenzyme Q10. Idebenone has a reduced lipophilic side chain and terminal hydroxyl groups that increase polarity and solubility. Because of this structure it can clear oxygen free radicals acting as an electron carrier and serve as an antioxidant [69].

Due to the nature of its structure, several groups have investigated the effect of idebenone on mitochondrial functions. Giorgio et al., in 2012 showed that idebenone can restore the ATP production in HQB17 and RJ206 cell cybrids after complex I and complex II inhibition. Moreover, idebenone reduces the rotenone-induced lipid peroxidation as well as the level of glutathione and superoxide dismutase (SOD) which play an important role in the antioxidant defence [70]. Idebenone also has a positive effect on mitochondrial stress enhancing mitochondrial clearance via mitophagy in a PD mouse model. In fact, an increased level of PINK1 and Parkin, as well as VDAC1 and BNIP3 have been shown after idebenone treatment, suggesting a potential role of this molecule in the autophagic flux [71].

The Zhejiang University study is investigating the effect of Idebenone after 24 months of treatment. The aim is to evaluate if this treatment may slow the progression of PD.

Title : A Study of Efficacy and Safety of Idebenone vs. Placebo in Prodromal Parkinson Disease (SEASEiPPD)

Phase : 2/3

Status : Recruiting

Clinical Trial ID : NCT04152655

Sponsor : Second Affiliated Hospital, School of Medicine, Zhejiang University

Study design : A multicenter, randomised, double-blind, placebo-controlled study of idebenone at 180 mg daily and 360 mg daily for 24 months for the treatment of early-stage Parkinson's disease with motor and non-motor symptoms.

Outcome measure : The primary outcome is to assess changes in MDS-UPDRS scores after 24 months.

Secondary outcome is to assess dopamine transporter levels in the striatum after 12 and 24 months, using dopamine transporter positron emission tomography.

Comments : This is the first trial for idebenone in PD and it will be interesting to see its effect on both motor and non-motor symptoms. However, it is important to mention that idebenone has been associated with mild hypotensive effects as well as ROS production, depending on its redox state [72, 73]. Moreover, a high dose is required for a therapeu-

tic effect [74] and at the moment there is a lack of consistent evidence for therapeutic effects [75].

Nicotinamide Riboside

Background : There are 5 clinical trials testing Nicotinamide riboside (NR) in PD. 3 of them are completed and the other 2 are recruiting (Table 1), these are summarised below in Table 3. 3 papers have been published assessing NR effect on PD.

NR is a member of the vitamin B3 family. In cells, it is readily converted into nicotinamide adenine dinucleotide (NAD+). NAD+is a critical regulator of NAD+-dependent enzymes that mediate cellular signalling pathways related to metabolism and mitochondrial function. Declining NAD+concentrations in tissue is a pathological factor in various ageing-associated diseases, with the brain being particularly vulnerable due to the high energetic demand of neurons.

NR has shown strong efficacy in animal models and has improved key features of neurodegenerative disorders, including mitochondrial dysfunction. Moreover, NR rescues mitochondrial defects in iPSCs-derived neurons, increasing mitochondrial mass as well as mtDNA, and decreasing the mitochondrial ROS level [76]. The NADPARK study demonstrated that orally NR administration is safe. Furthermore, they have shown that NR is able to increase the cerebral NAD levels (although 3 patients have shown no evidence of NAD increase). Interestingly, patients showing $a > 10\%$ increase in cerebral NAD had significantly improved UPDRS scores suggesting improved symptoms. Tissue samples were analysed to further understand the effect NR was having. Peripheral blood mononuclear cells and muscle samples showed elevated metabolites and an upregulation of oxidative phosphorylation related genes [77].

The clinical trial NCT03568968 by the Haukeland University Hospital is interesting because they are testing NR in early PD with the aim to slow the progression of the disease by preventing the NAD-deficiency which is a key-event in the pathogenesis of PD.

In the NOPARK study they tested a double-blinded clinical trial investigating if NR can be used as an oral administration, and if it is safe. Moreover, they evaluated the effect of NR on cerebral metabolism in PD. In this study they have demonstrated that NR administration is safe and leads to an increased level of cerebral NAD. However, the cerebral NAD response is variable and related to the individual person (e.g. 3 patients showed no cerebral NAD increase at all).

Title : NAD-supplementation in Drug naïve Parkinson's Disease (NAD-PARK)

Phase : N/A

Status : Completed

Clinical Trial ID : NCT03816020

Sponsor : Haukeland University Hospital

Study design : Randomised double-blinded study. 30 Participants randomised in 1 : 1 ratio to either vitamin supplementation (1000 mg daily) or placebo for 4 weeks.

Outcome measure : The primary outcome was to assess the differences between Parkinson's disease related pattern (PDRP) and placebo measured by FDG-PET comparing baseline and 3–4-week follow-up measurement.

The Secondary outcome was to assess clinical changes measured by MDS-UPDRS from using NR.

Comments : Nicotinamide riboside shows no side effects after administration [77]. Its positive effect on the mitochondrial function, in particular on the mitochondrial ROS, is definitely an asset for this molecule. Moreover, vitamin B3 helps to keep the nervous system, as well as the gut microbiota, in a healthy state [53]. NR seems to be a potential molecule to rescue pathological defects in PD, however results have not been published yet, but it is unlikely that a marked clinical change in the MDS-UPDRS will be observed due to the short treatment period in this trial. Finally, this supplement is currently available on the market so provided the results are positive it could reach patients quickly.

Ganoderma

Background : There are 2 clinical trials testing Ganoderma in PD (one recruiting and one completed) testing its effect on disease progression in PD patients as well as the safety of this compound in patients with early PD (Tables 1 and 4). 5 papers have been published assessing Ganoderma effect on PD. *Ganoderma lucidum (*Gl), also known as Lingzhi, is a fungus derived substance which has been shown to protect neurons from oxidative stress.

Gl is a white-rot fungus largely used in traditional Chinese medicine. It contains several bioactive molecules i.e. polysaccharides, triterpenoids, adenosine and sterols with many beneficial effects. The main action of Gl is as an antioxidant. Indeed, it has been shown that GI increases the activity of antioxidant enzymes including glutathione peroxidase (GPx), catalase (CAT) and manganese-superoxide dismutase in cardiac, hepatic and cerebral mitochondria of aged mice. Moreover, GI also increases the level of mitochondrial α-ketoglutarate

dehydrogenase (α-KGDH), pyruvate dehydrogenase (PDH) as well as complex I and II activity [78, 79]. Ren et al., (2019) have shown that GI treatment has a positive effect on the mitochondria, improving the electron transport chain efficiency as well as the ATP production and decreasing the ROS level in mice neuronal cells. In addition, GI rescued the level of protein involved in the mitophagy pathway such as AMPK, ULK1 and PINK1 suggesting a positive modulation of the mitochondrial clearance [80].

The pilot study by the Xuanwu Hospital in Beijing is the first study to be completed for GI. In this study the primary outcome tested the effect of GI on non-motor symptoms of PD and the secondary outcome assessed GI's effect on PD progression in terms of cognition, mood and quality of daily life.

Title : Efficacy and Safety of Lingzhi in Patients with Early Parkinson's Disease

Phase : 2

Status : Completed

Clinical Trial ID : NCT00224263

Sponsor : Xuanwu Hospital, Beijing

Study design : A Randomised, Double-Blind, Placebo-Controlled, Dose-Finding Study to Assess the Efficacy and Safety of Lingzhi in Patients with Early Parkinson's Disease Receiving Stable L-dopa/DCI. 360 participants were treated with either Lingzhi (dose is not reported) or a placebo for 12 months.

Outcome measure : The primary outcome was to assess motor function improvements. The secondary outcome was to measure patients' cognition, mood and quality of daily life.

Comments : *Ganoderma lucidum* is a very interesting molecule with several beneficial effects. It is quite well documented for its wide range of effects which include many mitochondrial functions as well as non-mitochondrial ones (e.g., immunomodulatory). However, it seems to be ineffective at postponing the progression of depression in patients with early PD [81], suggesting that other strategies may be needed to reduce depression symptoms in early PD. The Beijing study is exciting as they are investigating the effect of GI on the motor function in a large cohort of patients over a whole year, increasing the likelihood that a positive effect may be identified. The potential effect of GI on the patient's cognition and quality of daily life is very engaging. However, no results have been posted yet. GI is already available on the market, and it represents a potential molecule to attenuate the detrimental effects related to PD.

Isradipine

Background : There are 3 completed clinical trials for isradipine in PD and no ongoing trials (Table 5). 19 papers have been published testing isradipine against multiple models of PD.

Isradipine is an FDA approved dihydropyridine calcium channel antagonist that treats high blood pressure. Ca^{2+} influx through calcium channels in neurons stimulates mitochondrial metabolism to increase bioenergetics to meet demands. However, prolonged Ca^{2+} influx can result in extended mitochondria enhancement leading to the production of ROS, which damage components of the cell. Isradipine attenuates this Ca^{2+} influx.

It was discovered that chronic treatment of isradipine reduces mitophagy and mitochondria oxidative stress and increases mitochondrial mass [82], suggesting a reduction in enhanced mitochondria activity and thus damage. Isradipine also prevented neuron loss and PD symptoms in the 6-OHDA zebrafish model [83] and the MPTP mouse model of PD [84].

The first phase 2 clinical trial by Northwestern University was a small-scale trial to determine the safety of isradipine in pwp. The second phase 2 trial was larger, recruiting 91 patients and assessed dosage tolerability and efficacy of isradipine.

These enabled isradipine to reach phase 3 clinical trials. This trial enrolled 336 patients across 56 centres in the US and Canada with only 16 partic-

Table 5
List of Isradipine clinical trials

Clinical Trial ID	NCT00753636	NCT00909545	NCT02168842
Phase	2	2	3
Status	Completed	Completed	Completed
Sponsor	Northwestern University	Northwestern University	University of Rochester
Objective	To assess the safety and tolerability in pwp	To determine a dosage that is well tolerated and effective as slowing motor symptom progression	To assess the effect on motor and non-motor symptoms in recently diagnosed patients
Completion Date	February 2010	February 2012	November 2018

ipants dropping out. Each participant was assessed over 36 months and required to test their blood pressure twice daily as a precaution due to isradipine's role as a blood pressure medication. 5 mg isradipine tablets were taken twice daily for the course of the trial.

Title : Efficacy of Isradipine in Early Parkinson Disease

Phase : 3

Status : Completed

Clinical Trial ID : NCT02168842

Sponsor : University of Rochester

Study design : A multi-centre, double-blind placebo-controlled parallel group study of isradipine as a disease modifying agent in patients with early Parkinson disease. 170 patients were given 5 mg twice daily for 36 months, while 166 patients were on the placebo.

Outcome measure : The primary outcome measures were to assess isradipine's ability to slow the motor symptom progression of patients by assessing their MDS-UPDRS scores at 0 and 36 months.

Secondary outcome measures were assessed as the change from baseline to 36 months in the following:

- medication, for example levodopa dose, to determine progression of motor symptoms
- each section of the UPDRS assessment individually, to measure motor and non-motor symptoms separately
- modified Rankin score, ambulatory capacity and Parkinson's disease questionnaire 39 to measure the level of disability
- Montreal cognitive assessment to detect mild cognitive impairment
- Beck depression inventory score to measure depression and mood

Comments : Isradipine failed to meet primary outcomes. Researchers hypothesised a mean change in UPDRS score of 4 points difference, but after 3 years the scores only differed by -0.27. Isradipine was still considered safe with only 7 patients dropping out due to sustained low blood pressure. Adverse effects identified were dizziness and peripheral oedema, both of which are possibly related to a drop in blood pressure [52]. Despite initial disappointment, further in-depth analysis of the data showed that isradipine is removed from the body at different rates for different patients. Those who had slow removal and thus longer exposure to a higher concentration of isradipine had a reduced risk of needing antiparkinson treatments, such as levodopa. Examination of patient symptomatic changes revealed that as isradipine exposure decreased, non-tremor-related symptoms, such as bradykinesia, rigidity, gait and postural imbalance, worsened [85]. Although isradipine did not significantly prevent the progression of disease in all patients, it appears to be beneficial in a subset of patients and should still be considered for future studies in subgroups of PD patients that display mitochondrial dysfunction. Interestingly, nilvadipine, another calcium channel blocker, is currently part of a multi-arm, multi-stage phase 2 clinical trial [ACTRN12620000560998] [86]. Nilvadipine's calcium regulation ability and structural similarity to isradipine suggests it may modulate mitochondrial activity, however, we were unable to find any literature reporting a preclinical benefit.

EPI-589

Background: There is one clinical trial for EPI-589 in PD testing its safety and biomarkers in PD. It is an open-label study with a 30-day run-in phase and adaptive design component to include more participants. Two papers have been published assessing the effect of EPI-589 on amyotrophic lateral sclerosis (ALS) (Nothing has been published so far about the effect of EPI-589 on PD).

EPI-589 is an antioxidant molecule with free radical scavenging activity which protects against oxidative stress. Its reduced form can scavenge free radicals. EPI-589 is also able to oxidise itself back to its original form [87]. It has been demonstrated that EPI-589 protects against oxidative stress and prevents the 8-hydroxy-deoxyguanosine increase in urine [88].

This study by Edison Pharmaceuticals Inc is the first study to be completed for EPI-589. In this study they tested the safety of EPI-589 in PD patients as well as EPI-589's potential to alter the biochemical signature of PD by assessing peripheral blood biomarkers, central nervous system (CNS) biomarkers, and urine biomarker analysis.

Title : Safety and Biomarker Study of PTC-589 in Participants with Parkinson's Disease

Phase : 2

Status : Completed

Clinical Trial ID : NCT02462603

Sponsor : Edison Pharmaceuticals Inc

Completion Date :

Study design : A single group assignment to assess safety and biomarker study of EPI-589 in mitochondrial subtype and idiopathic PD subjects treated with 1000 mg daily for 3 months.

Outcome measure : The primary outcome was to assess the number of participants with Drug-Related Serious Adverse Events (SAEs). The time frame was to determine the baseline up to 30 days after the last dose of study drug (up to 4 months). The secondary outcomes were to measure after 3 months the changes from baseline in:

- Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Non-motor Symptoms Scale (NMSS)
- Parkinson's Disease Questionnaire - 39 (PDQ-39)
- EuroQol-5 Dimension (EQ-5D)
- Montreal Cognitive Assessment (MoCA) Score
- Beck Depression Inventory (BDI) Score
- Montgomery and Asberg Depression Rating Scale (MADRS)
- Maximum Observed Plasma Concentration (Cmax) of PTC589
- Level of Disease-Related Biomarker (Glutathione) in Plasma
- Level of Disease-Related Biomarker (Glutathione) in Cerebrospinal Fluid (CSF)
- Level of Disease-Related Biomarker (Glutathione) in Urine

Comments EPI-589 is an antioxidant molecule which has been tested in patients with ALS. Considering its similarity in structure to ubiquinone we may hypothesise that it influences mitochondrial complex III activity. However, at the moment there are no studies highlighting this potential mechanism. The therapeutic potentiality of this molecule may be interesting considering its effect as an antioxidant. Importantly, Noda et al., 2022 reported no differences between EPI-589 or placebo treated healthy controls, suggesting that EPI-589 administration has no adverse effects. In fact, the Edison Pharmaceuticals Inc showed that none of the 41 treated participants suffered any severe adverse event during the 30 days following treatment.

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