

## Can we prevent Parkinson's disease?

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## 1. ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 1 million people in the United States. Although the cause of PD remains unknown, a number of factors that increase the risk of developing this disease have been identified. Other factors that may prevent or slow down PD development and progression have also been found. In this review, we describe current basic, clinical and epidemiological findings on risk and neuroprotective factors and discuss how they can affect PD.

## 2. INTRODUCTION

### 2.1. Defining Parkinson's disease (PD)

Parkinson's Disease (PD) is the second most prevalent chronic neurodegenerative disorder in the United States (1). Individuals with PD display decreased longevity and have a mortality rate three times higher than that of normal age-matched individuals (2). The pathological hallmark of PD is the loss of neuromelanin-containing dopaminergic neurons within the substantia nigra pars compacta (SNpc) and the presence of fibrillary cytoplasmic inclusions, known as Lewy bodies, which contain ubiquitin

and alpha synuclein. As dopaminergic nigral neurons project to the striatum, the loss of these cells reduces striatal dopamine (DA). PD symptoms are typically described as motor ones, associated with dopaminergic nigrostriatal cell loss. They include resting tremor (mainly in the hand and forearm, (described as 'pill-rolling' type), bradykinesia (slowness of movement), hypokinesia (decreased amount of movement), rigidity (increased muscle tone) gait disturbances, and postural instability, all of which become more severe as the disease progresses (Table 1; 2,3,4,5,6). As PD pathology is not limited to the nigrostriatal system (7), non-motor symptoms, like arrhythmias and constipation are also observed (Table 1) Some investigators propose that the peripheral pathology is where PD starts (8). Dopamine replacement with levodopa remains the standard and often primary treatment for PD patients. In addition as PD progresses patients' response to this drug weakens and disabling side effects such as dyskinesias (abnormal movements) along with "on-off" motor fluctuations emerge (9).

PD is diagnosed by presenting two out of the three classical motor features (bradykinesia, rigidity,

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**Table 1.** Parkinson's disease symptoms

<b>Motor Symptoms</b>
akinesia (absence of normal unconscious movements)
decreased size and speed of handwriting
decreased stride length while walking
freezing (the inability to begin voluntary movement)
hypokinesia (reduction in movement amplitude)
hypomimia (paucity of normal facial expression)
<b>Nonmotor Symptoms</b>
addictions
anxiety
apathy (showing no interest or concern)
cardiovascular dysautonomia
constipation
dementia (especially in older patients)
depression,
drooling
falling asleep while driving
fatigue
genitourinary problems
hypophonia (decreases voice volume)
insomnia (chronic inability to fall asleep)
mania/hypomania (manifestation of bipolar disorder)
olfactory disturbances
painful or unpleasant sensations
pathologic gambling
personality changes
sexual disturbances
sleep apnea syndrome (temporary suspension of breathing occurring repeatedly during sleep)
slowed cognitive processes
sudden uncontrollable somnolence (sudden drowsiness)
thermal dysregulation

resting tremor), a strong positive response to levodopa, unilateral onset, and the absence of any of the disorders listed in Table 2. In contrast to PD, parkinsonism is defined as a combination of any of the classical motor features resulting from an identified cause, including other disorders as listed in Table 2 (10). However, there is no definitive diagnosis of PD as only 80% of cases clinically diagnosed, after postmortem analysis have the neuropathologic features of both Lewy bodies and dopaminergic nigral neuronal loss (11).

Since PD is an insidious, multisystem disease, misdiagnoses and underdiagnoses are not uncommon (12). Neither presymptomatic diagnosis of idiopathic PD nor effective biomarkers of disease progression exists. Proposed presymptomatic diagnostic tools include assessments of genetic background, autonomic function, and olfaction (13, 14), either with or without *in vivo* imaging of the dopaminergic system. Changes in specific gene expression signals in the blood are being evaluated as potential biomarkers of PD (15, 16).

### 2.2. PD demographics

Approximately 1 million Americans have PD based on previous annualized age- and gender-adjusted

research (17). PD is more prevalent (number of individuals in a population who have the disease at a specific point in time) in North America and Europe than Asia and Africa (18). In a study investigating PD in a multiethnic population (17) the age- and gender-adjusted rate per 100,000 was highest among Hispanics (16.6 per 100,000), followed by non-Hispanic Whites (13.6 per 100,000), Asians (11.3 per 100,000) and Blacks (10.2 per 100,000). These findings suggest that the incidence of PD varies by race/ethnicity. The overall risk of PD increases with advancing age. Only 0.5% of the cases were diagnosed with PD before age 40 and 3.4% before age 50. Over 60% of the cases were first diagnosed between age 65-79 (17). Males are at a 1.5 greater risk for PD than females (19).

### 2.3 Cause vs. risks and mechanisms of cell death in PD

The cause of PD (what starts the disease) has not yet been identified. This is probably because rather than a single etiology, a combination of variables overtime may trigger the onset of PD. Epidemiological studies have identified several risk factors for PD (those that increase the chance of developing the disease). Genetics seems to have a role, as gene mutations have been found in familial PD. This line of research has shed light to the possibility that impairment of the ubiquitin-proteasome system (UPS), intracytoplasmic protein accumulation and misfolding can

**Table 2. Differential diagnosis of Parkinsonism**

<b>Idiopathic</b>
Parkinson's disease
<b>Symptomatic</b>
Drug-induced (neuroleptics, presynaptic dopamine blockers, certain anti-emetics)
Hydrocephalus
Metabolic (hepatocerebral degeneration, parathyroid disorders)
Neoplasm
Postencephalitic parkinsonism
Post-traumatic parkinsonism
Toxin (carbon monoxide, manganese, MPTP)
Vascular parkinsonism
<b>Neurodegenerative</b>
Alzheimer's disease
Cortical-basal ganglionic degeneration
Dementia with Lewy bodies
Multiple System Atrophy (olivopontocerebellar atrophy, Shy-Drager syndrome, striatonigral degeneration)
Parkinsonism-dementia-ALS complex of Guam
Progressive supranuclear palsy
<b>Hereditary Disorders</b>
Familial parkinson's disease
Dentatorubral-pallidoluysian atrophy
Huntington's disease
Neurodegeneration with brain iron accumulation (Hallervorden-Spatz)
Wilson's disease
Spinocerebellar ataxias
<b>Other</b>
Psychogenic

Modified with permission from (16)

lead to cell loss. Aging and environmental factors may also facilitate cell loss in PD through mechanisms of excitotoxicity, disturbed calcium homeostasis, inflammation, oxidative stress, mitochondrial dysfunction or distressed energy metabolism. Evidence of these different cell death pathways have been found in the brains of PD patients (2, 20, 21, 22, 23, 24, 25). Overall a certain pattern is emerging linking mitochondrial dysfunction and oxidative stress to UPS impairment, intracytoplasmic protein accumulation, protein misfolding and inflammation, resulting in a slow destructive cycle of ongoing, progressive damage (26).

Promoters of cell survival for PD emerge as factors that have the capacity to counteract the mechanisms involved in neurodegeneration, ultimately affecting PD development and progression. Several factors that seem to decrease PD incidence have been identified and in many cases, are simple life style choices. This review will analyze current basic, clinical and epidemiological findings on risk and neuroprotective factors and discuss how these factors can affect PD development.

### 3. INCREASING THE ODDS OF DEVELOPING PD: RISK FACTORS

Risk is generally defined as the possibility of loss, injury, disease, or death. In this review, we define risk

factors as those that increase the chance (greater than in aged-matched controls) that someone will develop PD. Although epidemiologists cannot find a single cause of PD, studies have identified certain factors that increase the incidence of PD.

#### 3.1. Aging

Old age has been identified as a critical risk factor for the development of PD (11), probably because the nervous system is affected by aging. Decreased extracellular brain volume and total brain weight are typically observed with increasing age (27,28). Age-related declines in dopaminergic nigrostriatal function and motor behavior have been reported in normal human and non-human primates (29, 30, 31, 32, 33). Mild parkinsonian-like signs are commonly seen in the elderly (34, 35), although it should be mentioned that medical conditions such as arthritis or peripheral neuropathy can induce symptoms that resemble PD (34).

Cellular changes observed with aging may play a role in the neurodegeneration leading to PD (2, 4). Similar to PD, increased oxidative stress and mitochondrial damage seem to be part of the aging process (36, 37). Increased microglial activation, typical of PD pathology, is also observed with old age (27). This suggests that the aged brain is in pro-inflammatory state. In that respect, old primates show a rise in expression of antigenic markers of activated microglia including major histocompatibility complex (MHC)-class II antigen (an antigen significant in myelin; 28), CD4 positive antigen (27), and human leukocyte antigen-D receptor (HLA-DR; 38). Rodents also show an age-dependent increase in microglia expression in the brain (39). Microglial cell morphology is also affected by age, presenting cytosolic inclusions and hypertrophy of the cytoplasm. Since microglia are found in high density in the substantia nigra, their age-related dysfunction may affect nigral microenvironment increasing neuronal vulnerability to PD onset (40, 41).

Another age-related change that it is hypothesized to favor PD development is variation in cellular production of neurotrophic factors. These proteins are responsible for the growth and survival of neurons during development and for maintaining adult neurons (42, 43). Glial-derived neurotrophic factor (GDNF; 44), has been identified as a potent neurotrophic factor for dopaminergic neurons. Rodents show a decrease in striatal GDNF levels in aged animals compared to young ones (45). In monkeys with stable unilateral parkinsonian lesions (3 months after neurotoxin administration) no changes were observed in striatal GDNF levels with age (43). Gene expression of GDNF in humans is low or undetectable in normal and PD adult individuals (44). The role of GDNF in PD pathophysiology remains to be elucidated.

#### 3.3. Genetics

A number of PD cases (5%) have been identified to be genetically related, inherited by mendelian traits (2, 3, 46) and have been grouped as familial PD. While they are

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similar to sporadic PD, in general they begin at an earlier age and present atypical features (3). Familial forms of PD have been associated to mutations on 10 distinct gene loci including PARK1 (SNCA), PARK2 (parkin), PARK3, PARK4 (SNCA), PARK5 (UCH-L1), PARK6 (PINK1), PARK7 (DJ-1), PARK8 (LRRK2), PARK10, and PARK11 (24).

Alpha synuclein is a protein found in the normal brain that it is believed to modulate synaptic vesicle and DA neurotransmission, vesicle trafficking and cytoskeletal functioning (2, 47, 48). Interestingly, alpha-synuclein is typically found in Lewy bodies (the pathological hallmark of PD) and its mutations are associated with familial early onset PD (49). Studies suggest that alpha-synuclein mutations (PARK1 and PARK4) decrease lipophilicity, which consequently promotes protofibril formation (protein misfolding), Lewy body formation and cytotoxicity (46). Linkage studies have revealed triplication of the alpha-synuclein gene in some familial cases of PD, which suggests that accumulation of alpha-synuclein increases the risk of PD (51). Furthermore, alpha-synuclein aggregates inhibit functioning of the UPS, impairing detoxification and degradation of defective proteins (52). Consequently, this impairment creates a positive feedback mechanism whereby misfolded alpha-synuclein continues to accumulate and form aggregations increasing vulnerability to deleterious effects of other misfolded proteins (53).

Parkin, DJ-1, PINK1 (PTEN-induced kinase-1) are missense mutations that are found in autosomal recessive and some sporadic PD cases (2, 3, 24, 26). They are also thought to be involved in mitochondrial function and reaction to oxidative stress (46). Parkin and PINK1 use the same genetic pathway to regulate mitochondrial function, whereas DJ-1 functions as part of a separate pathway (54). The onset of Parkin-related PD usually occurs before age 30 (2, 3), is most common in familial, but is also found in sporadic PD cases (24). DJ-1 mutations account for only a small portion of the early onset PD cases, but is the second most frequent cause of recessive forms of PD after Parkin mutations (3).

In contrast to the Parkin, DJ-1 and PINK-1 genes, where mutation leads to loss-of-function and development of PD, the Leucine-rich repeat kinase 2 (LRRK2) gene mutation has been shown to increase its autophosphorylation and substrate phosphorylation. LRRK2 is part of the MAPKKK family, which is thought to function in a programmed cell death pathway. Post-mortem cases of LRRK parkinsonism exhibit typical Lewy body disease consistent with the pathology of PD (46). Additionally, LRRK2 mutation carriers have characteristic nigral degeneration and are thought to display severe cognitive changes, along with exhibiting a more severe progression of PD (55). The most common mutation is Gly22019Ser, leading to frequent substitution in Caucasians, which explains 1-2% of cases of sporadic PD (46, 56). Pathogenic mutations of LRRK2 have recently been strongly linked to PD in certain populations (20-40% of PD in Ashkenazi Jews and north African Arabs) (57). Gly2019Ser is also an age-dependent mutation, which

increases from 17% at age 50 to 85% at age 70 (46). The role of LRRK2 in modulating PD pathology is still a puzzle and researchers are continuing to elucidate the pathways of cellular stress, inflammation, and apoptosis, which mutations of this gene could be involved in.

### 3.4. Environmental factors

The identification of 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridinium (MPTP), as a human parkinsonian toxin brought awareness to the role of environmental factors in the development of PD (58, 59). MPTP nigral toxicity has been confirmed in the lab and has been used to develop animal models of PD, which have become powerful tools for investigating PD (2, 4, 60). MPTP brain toxicity depends on becoming the electrically charged molecule, MPP<sup>+</sup>, a reaction catalyzed by monoamine oxidase-B (MAO-B). MPP<sup>+</sup> is transported into dopaminergic cells by the dopamine transporter (DAT), where it interferes with complex I of the mitochondrial electron transport chain, affecting cell energy production and causing buildup of free radicals. (61).

MPTP was originally developed as an experimental herbicide chemically related to paraquat (2). Like MPTP, paraquat is a mitochondrial complex I inhibitor (4). In 1985, Barbeau and colleagues investigated the relationship between the use of paraquat and the incidence of PD and found paraquat use to be significantly associated with PD (62). The highest prevalence of PD was found in northern states, mid-Atlantic, upper midwestern states, and Pacific coast states which closely overlap with areas of highest use of pesticides. Follow up studies have found that occupational exposure to herbicides, insecticides (not with rodenticide or acaricide), is associated with as much as a 70% increased chance of developing PD than if someone did not use chemical killers (4, 15, 63, 64). Rural areas with farming and consumption of well water are associated with increased risk of developing PD (4). In that regard rotenone, a naturally occurring garden pesticide derived from the roots of tropical plant species, including lancepod, barbasco, and tuba plant, is commonly used as an insecticide and as fish poison (2, 4). Similarly to MPTP and paraquat, rotenone is a mitochondrial complex I dysfunction agent and in rodents it can induce dopaminergic nigrostriatal degeneration, abnormal posture and slowness of movement (2, 4, 60). Other groups of pesticides such as organochlorines, organophosphates, carbamates, and pyrethroids are associated with increased incidence of PD as well. Current research suggests that prenatal exposure to these environmental toxins may increase susceptibility to developing PD later in life (5, 65).

It is controversial by which mechanism prenatal exposure to an agent increases PD risk. A possibility is that exposure to a toxin that kills dopaminergic neurons, decreases the pool of DA cells and the plasticity of the system to respond to challenges overtime. Although this theory explains increased risk, it fails to elucidate disease progression. One alternative explanation is that the toxin, in addition or instead of inducing cell loss, alters the system homeostasis, locally increasing inflammatory cytokines

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which attracts activated microglia that produces nitric oxide (NO<sub>2</sub>). In turn NO<sub>2</sub> increases oxidative stress, taxes energy metabolism, affecting mitochondrial function and so on. It is currently being studied whether women with bacterial vaginosis while pregnant may lead to a pro-inflammatory state in the fetus, which may make it more susceptible to dopaminergic cell loss after exposure to dopaminergic neurotoxins (30, 66). This concept is plausible as inflammation is a key finding in parkinsonian brains. Evidence for a possible role of chronic inflammation in PD development following infection is encephalitis lethargica (EL), also known as Von Economo's encephalitis. Post Encephalitic Parkinsonism (PEP) was first reported in 1917 during an epidemic of EL. DA depletion is exhibited in the zona compacta of the substantia nigra (67). PEP patients respond to levodopa, however as in PD, sensitivity decreases over time (68).

### 3.5. Head trauma

There are several studies indicating that head trauma substantially increases the risk of PD (69, 70, 71). In a retrospective study of 196 PD patients with age-matched controls, there was a significant increase in the frequency of head trauma among PD patients than controls (70). One explanation proposed to account for this association is recall bias; that is PD patients are more likely to remember past head traumas than matched controls (11). However, laboratory studies have demonstrated that chronic head injury impairs energy metabolism, increases oxidative stress, and neuroinflammation, leading to nigrostriatal damage (11). This type of chronic head trauma may also explain why there is correlation between boxing and an increased risk of developing PD (71). Prospective studies are necessary to critically evaluate the association between head trauma and the risk of PD.

### 3.6. Comorbidities

PD comorbidities is an increasingly important topic as many diseases of interest such as type 2 diabetes (T2DM), Alzheimer's disease (AD), and cancer are on the rise. Like PD, they share risk factors, such as higher incidence in the elderly population. As they also present similar mechanisms of cell dysfunction and death it has been proposed that the different disorders maybe different manifestations of the same metabolic imbalance (26). Some of these disorders, as they may precede PD onset, have been proposed as risk factors for PD.

T2DM has reached epidemic proportions within the past forty years, and is associated with a variety of complications (72). T2DM is defined by insulin resistance, in which the pancreas produces enough insulin, but the body cannot use it effectively. Insulin is a hormone that is needed to convert glucose (coming from sugar starches or other food) into energy needed for daily life. In T2DM, inefficacy to use insulin means inefficacy to use glucose, which builds up in the blood. Like PD, T2DM is also common in aged individuals (73). Animal studies have reported that insulin can modulate dopaminergic activity, which is not surprising considering there is a high density of dopaminergic neurons and insulin receptors in the SN (74, 75). A decrease of insulin-receptor immunoreactivity

and mRNA and TH mRNA in the SNpc was found in PD patients (74). In a large prospective epidemiological study with 633 individuals, a significant positive correlation was found between T2DM and the risk of PD (68). Diabetic patients exhibit parkinsonian signs such as postural reflex impairment-gait disturbance (73). At the moment, it is still unclear the mechanism by which T2DM increases PD risk. A possible explanation is that insulin dysregulation and inefficient use of glucose could affect cell energy metabolism and mitochondrial function, imposing oxidative stress, and inflammation.

AD is a progressive neurodegenerative disorder characterized by loss of cognitive function. Its cardinal pathological features include amyloid plaques and the formation of neurofibrillary tangles (76). AD, like PD, is more common with old age and T2DM is a risk factor. Since there is a high rate of misdiagnosis of both PD and AD, especially during early stages of both diseases, a diagnosis for the coexistence of PD and AD in an individual is even less accurate (77). This is complicated by the fact that a number of PD patients develop cognitive disorders as the disease progresses (78). Reports of the coexistence of AD with PD indicate increase in mortality (78). Pathologically confirmed cases of PD with co-existent AD pathology had a mean survival of approximately 4.5 years (78). There is evidence that AD and PD share many of the same molecular mechanisms of neuronal damage including oxidative stress and programmed cell death (79). Pathological evidence that supports comorbidity between PD and AD includes the presence of Lewy bodies in some AD cases, and the ability of alpha-synuclein to facilitate tau phosphorylation (77) which leads to fibrillary tangle formation.

Researchers are also examining the relationship of cancer to PD. Cancer occurs when alterations in cell physiology (self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replication, and angiogenesis) cause malignant growth (80). These cell mutations are more common with old age. Whether cancer increases or decreases the risk of PD is not clear. Mortality studies show a decrease in death of cancer patients with PD than those in the general population (81). Most cancers appear to be less common in patients with PD. However, there are a few types of cancer where the inverse relationship is true, including malignant melanoma (82, 83), thyroid (84), and breast carcinoma (85). PD gene mutations have also been associated with cancer. Parkin mutations are correlated with tumorigenesis including breast and ovarian tumors (80). DJ-1, not only is mutated in forms of PD, but is also an oncogene, which is overexpressed in carcinomas (86).

## 4. NEUROPROTECTIVE FACTORS

Neuroprotective factors are those that prevent or slow down neurodegeneration. A combination of epidemiological data and basic research is providing evidence of potential new ways to achieve neuroprotection

for PD using noninvasive treatments and/or lifestyle choices.

As we have previously described, PD is a multi-symptom, multi-system disease with neuropathological changes occurring in different areas of the central and peripheral nervous system (87, 88, 89). In that context, general or systemic neuroprotective approaches have a clear advantage compared to localized ones. Interestingly, as nigral cell loss is the most evident characteristic of PD, the main focus in PD research has been the SNpc.

### 4.1. Exercise

Emerging evidence suggests that physical activity may confer protective benefits for several neurological diseases, including PD (90, 91). Chronic physical activity has been associated with changes in neurotransmitter levels, the expression of endogenous neurotrophic factors, the growth of neuronal processes, and neurogenesis (90). In normal older adults, chronic physical activity has been shown to improve neurological health, increase the expression of neurotrophic growth factors, and have beneficial impact on depression, quality of sleep, and cognitive function (91). Although we cannot become younger and reverse the signs of aging, exercise has been shown to be the single most effective way to decrease or slow down the aging process (92).

Physical activity may have neuroregenerative and neuroprotective influences on the brain by stimulating the growth and development of new cells. The stimulation of these “self-repair” mechanisms may facilitate recovery after ischemic neuronal damage in the hippocampal formation, neurotoxic damage in the striatum, or traumatic brain injury (90, 91). During acute exposure to stress, exercise can mitigate several harmful consequences that are observable at different levels of function, including behavioral/emotional, immunologic, neural, and cellular levels (91). The intensity and frequency of physical activity seems to be important for effectiveness (91).

Given these neurobiological effects it is reasonable to hypothesize that motor activity may have preventive properties against neurodegenerative diseases (90). In that regard, animals challenged with DA neurotoxins that undergo intense physical activity, such as running, present reduced vulnerability of nigral neurons to oxidative stress (90). A prospective study of 143,325 participants (average age at baseline 63 years old) followed for 9 years showed a reduction in PD risk in the subjects that engaged in moderate to vigorous exercise (92).

As PD patients present motor impairments and balance disturbances, which increases the risk of falls or injuries, low impact exercise, like Tai Chi, are preferentially recommended (93, 94). Current evidence supports that any exercise is beneficial for PD patients with regards to physical functioning, health-related quality of life, strength, balance, and gait speed (95). New prospective studies are currently being developed to compare different exercise plans, including methods to

facilitate high impact activities, such as assisted running for PD patients.

### 4.2. Food and dietary supplements

As oxidative stress has been associated with cell death in PD a number of studies have focused on the effects of antioxidants in food and dietary supplements. Compared to other fruits and vegetables, blueberries are one of the richest sources of antioxidants, containing vitamins E and C, flavonoids, carotenoids, and numerous phytochemicals that exhibit antioxidant activity (96, 97). Dramatic positive results have been seen in aged rodents that consume as little as a 2% blueberry extract supplemented diet (96, 98). In a rodent model of stroke, blueberry supplementation ameliorates cellular damage (96), and blueberries have been shown to increase neurogenesis in the aged rat brain (86). Similarly, in a rodent model of PD, animals fed with blueberry-and spirulina-enriched diets had higher levels of striatal DA than those not given the dietary enrichment (97). Dietary supplementation with strawberry, spinach, or blueberry extract has shown improvements in calcium homeostasis in aged animals (96). An *in vitro* study examining freeze dried acai, reported a high oxidative scavenging capacity for the fruit, higher than any fruit or vegetable tested to date (99). This suggests acai is a powerful antioxidant and may therefore be potentially neuroprotective against PD. Green tea (98) and ginseng (97) are also rich in antioxidants and are currently being evaluated as neuroprotective therapies for PD. Red wine (100), dark chocolate (101), and olive oil (102) are notable sources of the potent antioxidant polyphenols and considered neuroprotective candidates. Ginkgo biloba is a plant extract composed of a complex chemical mixture that exerts neuroprotective effects against models of mitochondrial damage and oxidative stress (103). It also protects dopaminergic neurons from MPTP neurotoxicity, as does nicotinamide (104). Acetyl-L-carnitine delays mitochondrial depolarization in response to a variety of stressors, including oxidative damage (105). Lipoic acid shows significant improvements in mitochondrial function and cognitive tasks (23).

One of the first over-the-counter supplements to be analyzed was alpha-tocopherol (Vitamin E). In 1988, Golbe and colleagues (106, 107) reported its neuroprotective effects in PD patients. The prospective “Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism” (DATATOP) clinical trial failed to show neuroprotection by tocopherol, although deprenyl delayed the onset of disability (108). A new prospective analysis from the Nurses’ Health Study, showed consumption of high doses of vitamin E from food decreased PD risk. Investigators also found that carotenoids, vitamin C or multivitamins were not effective (109).

Ubidecarenone, also known as coenzyme Q10 (CoQ10), is a well-known antioxidant agent (6, 20, 21, 22, 110, 111, 112, 113). It directly scavenges free radicals in the inner mitochondrial membrane by acting as an electron shuttle for complex I and II of the electron transport chain (22). CoQ10 mitochondrial levels are significantly lower in patients with PD as compared to age-comparable

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controls (114). The loss of CoQ10 in PD patients correlates with mitochondrial dysfunction in PD. Plasma %CoQ10 in PD patients are greater than in controls, suggesting there is an increase in oxidative stress in PD patients (115). In a study where 28 PD patients were given oral CoQ10 360 mg daily for 4 weeks, there was a significant improvement in PD symptoms compared to the placebo. However, no improvement of motor symptoms or activities of daily living were seen (111). A randomized, double-blind, calibrated futility clinical trial of CoQ10 and GPI-1485 in early untreated PD using placebo data from the DATATOP study was performed to establish the futility threshold (116). The primary outcome measure (change in total Unified Parkinson's Disease Rating Scale scores over 1 year) did not meet the pre-specified criteria for futility for either agent. Secondary analyses using calibration controls and other more recent placebo data question the appropriateness of the predetermined definition of futility, and suggest that a more restrictive threshold may be needed. An independent large clinical trial of CoQ10 funded by NINDS is planned.

Uric acid (UA) is the final product of purine metabolism in humans and also a powerful antioxidant (117). Studies have shown that UA is not only a free radical scavenger, but can also be an electron donor, and an iron chelator (118). Epidemiological evidence suggests that high blood levels of UA decrease the risk of PD (8). In a large prospective study of 18,000 men, there was a 55% lower risk of developing PD among men in the top quartile of plasma urate concentration (119). Inosine, a urate precursor, is currently used in clinical trials for multiple sclerosis patients (119). A clinical trial to assess the effects of UA in PD patients, also using inosine, is currently underway. It should be noted that elevated urate levels increases the risk of having kidney stones and gout, as well as possible cardiovascular complications and its administration should be monitored by physicians.

Creatine monohydrate is a bioenergetic compound important in ATP homeostasis (120). Creatine converts to phosphocreatine and may act as an indirect antioxidant by facilitating energy transduction and mitochondrial permeability (121). Administration of creatine can prevent mitochondrial creatine kinases from being converted into the dimeric form and increases glutamate uptake into synaptic vesicles. Creatine may therefore protect against mitochondrial dysfunction in PD. In rodent models of PD, creatine attenuated dopaminergic neuronal loss (122). Creatine recently passed a phase II "futility" clinical trial and is now moving into phase III trial to determine if a purified medicinal form can slow PD progression (123). As creatine intake may induce stomachaches, diarrhea, increased urination and/or muscle cramps, its use should be properly supervised.

Glutathione is a major antioxidant and redox modulator in the brain. PD patients display decreases in total glutathione concentrations in the SNpc (124). The magnitude of reduction in glutathione levels seems to parallel the severity of PD and in advanced stages of the disease glutathione is undetectable in the SNpc (21). A

small, but statistically significant improvement in disability was found in PD patients that used glutathione (600 mg twice daily i.v.) compared to controls. Even after 30 days of therapy were completed and glutathione was discontinued, assessments were repeated monthly, and the therapeutic effect of glutathione was noted to last for 2-4 additional months after drug discontinuation. Unfortunately, there is currently insufficient evidence to recommend the use of glutathione since epidemiological studies have not confirmed these results (124).

Caffeine consumption is inversely associated with the risk of PD. The overall risk of PD is 30% lower among coffee drinkers compared to age-matching controls (125). Caffeine is a non-specific adenosine A<sub>2A</sub> receptor antagonist and has been reported to modulate DA release (126). In rodent models of PD, caffeine induced significant preservation of nigrostriatal DA and nigral dopaminergic neurons compared to vehicle (126, 127, 128). It is controversial if these positive effects are mediated via antagonism of A<sub>2A</sub> receptors, or by direct inactivation of apoptotic pathways (129).

Using multiple food items (such as blueberries, nuts or coffee) as sources of antioxidants are mostly safe when ingested in moderation as part of a balance diet. In comparison, supplements, even those that can be obtained over-the-counter, can have side effects (specially when ingested in high quantities). In addition, as over-the-counter supplements are not required to follow the strict standards expected from medications, the quality and quantity of the active ingredient used in their preparations may vary between brands, affecting their safety and effectiveness. To minimize their risks and maximize their advantages supplement use should be monitored by medical doctors.

### 4.3. Caloric restriction

A proposed alternative to healthy eating and dietary supplementation is long-term caloric restriction. This approach has been shown to reduce age-related diseases, while lowering cholesterol, fasting glucose, and blood pressure (130, 131, 132). Epidemiological studies have shown that people who follow a low-calorie, low-fat diet may be at a lower risk for PD. In the MPTP monkey model of PD, calorie restriction has also been shown to attenuate motor dysfunction, preserve levels of dopamine, as well as increase levels of GDNF (133). In other studies, caloric restriction has been found to prevent apoptosis by preventing caspase-1 activity (134). Caloric restriction also seems to be neuroprotective in rodent models for other neurodegenerative diseases such as Alzheimer's disease (135), Ischemia (136), and Amyotrophic Lateral Sclerosis (137). Based on this evidence, caloric restriction is one strategy to decrease the risk of PD, although it is unknown how caloric restriction affects PD patients who are already symptomatic (138).

### 4.4. Nicotine

The overall risk of developing PD is 60% lower among smokers (138). Nicotine is the active ingredient in cigarettes and has been identified as the responsible neuroprotective factor in smoking (139). Nicotine

stimulates nicotinic acetylcholine (nACh) receptors in the nigrostriatal system. Similar to dopaminergic transmission, there is a significant loss of nACh receptors in PD patients in this area (139, 140). Nicotine is involved in modulating DA release via nACh receptors. Therefore, if these receptors become downregulated in PD, there is also a reduction in DA release (139). In parkinsonian MPTP animal models, nicotine was reported to decrease nigrostriatal damage by stimulating DA release. DA and MPP<sup>+</sup> compete for the use of the DA transporter in the dopaminergic cell terminals. Thus, increased DA in the terminals decreases MPP<sup>+</sup> ability to induce intra-DA cell toxicity (141). Nicotine has also shown antioxidative properties, reducing free radicals (140). In animal models of PD agonists of nACh-alpha-7 receptor elicit neuroprotective effects, while agonists of nACh-alpha-4-beta-2 receptors modulate PD symptoms (142).

### 4.5. Anti-inflammatory compounds

Inflammation is a process by which the body's defense system (immune system) protects itself against infection and foreign substances (143). Inflammation in the brain involves microglia activation and secretion of chemicals named cytokines. The brain of PD patients, as well as animals and humans exposed to DA neurotoxins, typically present activated microglia in the nigrostriatal system. Aging (the most important PD risk factor) presents mild microglia activation resembling an inflammatory-like state (27). While inflammation is essential for survival, too much can be harmful, as increases oxidative stress and metabolic requirements. Based on this information anti-inflammatory treatments have been explored as a strategy to prevent PD progression.

Non-steroidal anti-inflammatory drugs (NSAIDs) induce their effects by inhibiting cyclooxygenase, an enzyme involved in the synthesis of pro-inflammatory prostaglandins (144). Numerous studies in animal models of PD have found that NSAIDs, such as ibuprofen, celecoxib, and rofecoxib have neuroprotective properties (145, 146, 147, 148). Clinical studies have also found that NSAIDs can have some benefits for PD. In a prospective analysis, aspirin or acetaminophen use was associated with a higher PD risk, yet aspirin use of less than or equal to 300 mg/day for more than 3 years was associated with a lower PD risk compared to no use (149). Intake of non-aspirin NSAIDs was associated with a 20% reduction in the incidence of PD among men and a 20% increase in the incidence of PD among women. The lower risk in men was especially marked for high doses and long duration of use. The risk in women was elevated for all indications. This study suggests that non-aspirin NSAID use reduces PD risk in men but not in women (149). Although these data are very interesting, the chronic use of NSAID has been shown to have serious side effects such as stomach ulcers, gastrointestinal bleeding, liver and kidney damage, and high blood pressure, suggesting that administration of NSAIDs should be supervised and patients should consult with their physicians before starting chronic administration (150, 151).

Another type of drug with anti-inflammatory properties is the tetracycline derivative minocycline.

Minocycline's anti-inflammatory actions are distinct from its mechanisms as an antibiotic. There is mixed data supporting minocycline's role as an anti-inflammatory agent against PD. In MPTP mouse models of PD, there are some reports that minocycline increases TH positive neurons in the SNpc, while inhibiting activation of microglia (152). However, other reports indicate that although minocycline decreased activation of microglia, it did not provide neuroprotection against MPTP (153). Despite mixed results in animal models, minocycline is currently being investigated in clinical trials for PD (154). It should be mentioned that a recent clinical trial evaluating the efficacy of minocycline in Amyotrophic Lateral Sclerosis patients reported adverse effects of the compound in a dose-dependent manner, such as gastrointestinal and neurological side effects (155).

One class of compounds that has recently garnered attention from scientists for its anti-inflammatory properties is thiazolidinediones, which are peroxisome proliferator-activated receptor-gamma agonists (PPAR-gamma). One type of PPAR-gamma agonist is the drug pioglitazone. Pioglitazone treats diabetes by stimulating insulin-mediated glucose transport and metabolism. In a mouse model of PD, pioglitazone attenuated microglial activation, decreased oxidative stress, and partially restored striatal DA (156). Evidence from primate models of PD as well have supported the concept that pioglitazone may have neuroprotective effects (157). It should be noted that rosiglitazone a compound related to pioglitazone has been associated with serious cardiovascular dysfunction, and that in general, there are warning labels for the use of glitazones (158).

### 4.6. Calcium modulators

Calcium channel blockers are widely used for a variety of disorders including high blood pressure, hypertension, and angina (159). Scientists are studying if these drugs can be neuroprotective in PD, as changes in calcium influx may affect nigral cell survival. Unlike other neurons in the brain, SNpc DA neurons run like pacemakers on an autonomously active basis with Cav1.3 subunit. (160). Additionally, SNpc DA neurons rely on L-type Ca<sup>2+</sup> channels. Normally in L-type Ca<sup>2+</sup> channels, calcium flows readily into cells and is pumped out through ATP membrane transporter occurring during action potentials. However, in the SNpc, Ca<sup>2+</sup> channels are open most of the time (160). Therefore, there is a larger influx of calcium, causing a greater burden to the neuron by increasing oxidative stress and cellular damage (160). This influx could facilitate aging of SNpc DA neurons, which is consistent with reports that a higher rate of SNpc DA neurons with increasing age (5-10% per decade) are lost than other types of neurons (161).

To combat calcium influx induced damage, Ca<sup>2+</sup> channel blockers are now being assessed for PD therapy. Flunarizine, cinnarizine, have been reported to decrease dopaminergic cells *in vitro* (162). In a retrospective study with 3,637 cases of PD patients with aged matched controls, chronic use of Ca<sup>2+</sup> channel blockers was



associated with a significant decrease in the risk of PD (62). Though this study elicited valuable results, a prospective study is imperative to determine if  $\text{Ca}^{2+}$  channel blockers can attenuate the progression of PD. It should be mentioned that some  $\text{Ca}^{2+}$  channel blockers may actually be harmful to PD patients.

### 4.7. Monoamine oxidase B (MAO-B) inhibitors

MAO-B inhibitors, such as selegiline (previously known as deprenyl) are used in PD treatment due to their ability to block DA from being metabolized, thus increasing DA availability (163). When it was proposed that the neurotoxin MPTP needed intracerebral MAO-B to convert to its toxic metabolite  $\text{MPP}^+$ , selegiline was used to test and confirm this theory (164). The neuroprotective properties of MAO-B were then further tested in clinical trials. Selegiline treated patients showed a delayed in the onset of disability suggesting neuroprotective effects (108). Recently, it was found that selegiline has antiapoptotic properties by upregulating bcl-2 and bcl-xl (165), suggesting that neuroprotection is not solely mediated by MAO-B inhibition. Selegiline also reduces oxidative stress by attenuating the production of oxidative radicals, upregulating superoxide dismutase and catalase, and decreasing iron mediated oxidation of DA (166).

Rasagiline is a second generation MAO-B inhibitor with potential neuroprotective properties for PD patients. Studies suggest that, like selegiline, rasagiline increases levels of bcl-2 and bcl-xl, which protects dopaminergic neurons against apoptosis (167). Studies in dopaminergic SH-SY5Y cell cultures (cells that lack MAO; 168) rasagiline also affected apoptosis by decreasing the accumulation of glyceraldehyde-2-phosphatase dehydrogenase induced by the neurotoxin N-methyl(R)salsolinol. In a meta-analysis of 63 clinical and laboratory studies of rasagiline, it was shown that when administered orally at 0.5-1.0 mg per day, it was effective, selectively inhibited MAO-B, and was well tolerated in PD patients (169).

### 4.8. Estrogen

The incidence of PD is higher in males than females (11, 19). Gender differences in sensitivity to neurotoxins have been observed. Studies in experimental animals suggest that estrogen acts as a neuroprotectant from numerous forms of injury (170). Gender differences have also been shown in response to treatment of PD, for example, in how levodopa is metabolized (women have greater levodopa bioavailability). A slight significant difference in disability between sexes and quality-of-life reporting was shown, as females stated increased disability and reduced quality of life (171). The results of retrospective surveys of the neuroprotective effects of estrogen replacement in PD are controversial, with some showing no effect on risk and others showing a reduction in risk. In the "PD On Estrogen Therapy Replacement in the menopause Years" (POETRY) study, participants were found to have improved scores on the Unified Parkinson Disease Rating Scale (171). Based on the POETRY results, it is hypothesized that estrogen replacement therapy may decrease PD symptoms and provide an opportunity to

reduce the prescribed amount of antiparkinsonian medication in females.

### 4.9. Trophic factors

GDNF has been identified as a potent DA neurotrophic factor during development and has neuroprotective effects in animal models of PD (172, 173). Therefore, GDNF is a logical candidate for PD treatment (174, 175). The receptor complex for the trophins of GDNF family comprises the transmembrane receptor tyrosine kinase Ret and an extrinsic protein receptor GRFalpha that acts as the binding element (176). There are four distinct GRFalpha subunits. GDNF preferentially bind to GRFalpha-1, which is abundant in DA nigrostriatal neurons. GDNF, as other trophic factors, is a large protein and cannot freely cross the blood brain barrier. In order to target the nigrostriatal system, clinical trials relied on surgical implantation of intracerebral cannulae to deliver GDNF directly into the brain. The controversial results of the GDNF trials revealed that the method of delivery and the dosing seem to be key elements to ensure the success and safety of the treatment (177, 178). New trials have been halted until new animal data are collected.

Neurturin, a homolog of GDNF with similar neuroprotective properties, has been proposed as an alternative trophic treatment due to its neuroprotective properties in animal models of PD (179, 180). Neurturin preferentially binds to GRFalpha-2 subunit (181). As these binding receptor subunits are scantily present in the nigrostriatal system (182), it is hypothesized that neurturin actions in dopaminergic neurons depend on nonspecific binding to GRFalpha-1 receptors. Similar to GDNF, neurturin cannot cross the blood brain barrier. To overcome this issue a current clinical trials uses intracerebral brain injections of viral vectors to introduce the neurturin gene in the neurons of the nigrostriatal system (in vivo gene therapy) and increase localized neurturin production (183).

Trophic factor delivery using surgical methods presents, in addition of the potential risks associated to the novel compound, risks associated to the invasive nature of the procedure as well as the delivery system. For example, cannulae and pump systems have an increase chance of infection, while viral vectors can introduce wild type viruses. At this time gene expression cannot be stopped in case of complications.

In order to facilitate trophic factor therapies, investigators are searching for methods to allow big molecules to cross the blood brain barrier. This will allow systemic delivery, avoid costly and risky surgical interventions and will enable administration earlier in the course of the disease. Trojan horses technology, such as the fusion of GDNF to the carboxyl terminus of the chimeric monoclonal antibody to the human insulin receptor are currently being investigated in animals (184). Systemic delivery of trophic factors may also prevent neurodegeneration beyond the nigral cells, affecting other regions compromised by PD. These potential benefits carry the risk of inducing side effects associated to

unwanted trophic factor receptor activation in non-desirable areas or disturbing the molecule system targeted by the trojan horse. Future clinical trials using these novel technologies will depend on their demonstration of safety

### 4.10. Other potential neuroprotective factors

Several other candidate neuroprotective factors are being considered at the present time. GM1 ganglioside is a component of neuronal membranes, which may mediate neurotrophic factors actions and inhibit apoptosis. Results in animal models of PD have been mixed (185, 186, 187). In a double-blind placebo-controlled study, GM1-treated PD patients showed an improvement in clinical motor ratings, daily activities, and some dimensions of neuropsychological performance (185). A disadvantage of this compound is that it must be administered parenterally. However, pharmaceutical companies are currently examining ways to deliver the compound orally.

GPI-1485 is a neuroimmunophilin ligand that interacts with the protein FK506 (188). This interaction activates neurotrophins without inducing the immunosuppression observed with other related compounds, such as cyclosporine A (188). As stated earlier, a clinical trial of CoQ10 and GPI-1485 in early untreated PD using placebo data from the DATATOP study was performed to establish the futility threshold. However, results were inconclusive (116). Consequently, future studies are needed to assess the clinical efficacy of GPI-1485 for PD.

DA agonists (compounds that act on DA receptors) such as ropinirole and pramipexole have been proposed to be neuroprotective, but results from clinical trials have been controversial (189). The "Comparison of the Agonist pramipexole versus Levodopa on motor complications of PD" (CALM-PD) study was undertaken to assess in early PD the effects of pramipexole supplemented with levodopa versus levodopa alone. Progression of nigrostriatal degeneration was monitored using [ $^{123}$ I] $\beta$ -carbomethoxy-3- $\beta$ -(4-iodophenyl)-tropane (beta-CIT) single photon computerized emission tomography (SPECT) at 2, 3, and 4-year time points. Beta-CIT is a radioligand of the DA transporter. Patients treated with pramipexole supplemented with levodopa showed significant upregulation of beta-CIT, suggesting higher neuronal density and a reduction in DA nigral cell loss (190, 191). A similar clinical study using ropinirole, and then imaged with 18-fluorodopa (a radioligand equivalent to levodopa) positron emission tomography (PET) elicited similar results to the CALM-PD trial (192). However in both studies is discussed the value of imaging as an indirect measure of neuronal survival and whether the experimental design was appropriate to eliminate potential confounding effects generated by the administration of PD medications (189).

## 5. CONCLUSIONS AND PERSPECTIVES

Can we prevent PD? Based on the data discussed in this review, proposing a "one size fits all" recipe for preventing PD is unwise. Accumulated evidence supports the concept that PD is a multi-etiological, multi-system

disease that presents with individual differences in symptoms and progression (87, 88, 193). Risk and neuroprotective factors seem to be part of the equation that defines who will ultimately develop this disease. Nobody chooses to get PD.

It cannot be emphasized enough the need to find predictive and diagnostic tools, as well as sensitive biomarkers of disease progression. Innovative screening methods may be able to identify people at risk of developing PD and biomarkers can help recognize PD very early, prior to extensive cell loss, when introduction of neuroprotective therapies can be the most beneficial. Biomarkers can also (ideally) provide unbiased clues to assess in a short period of time if a therapy is modifying the course of PD or is just affecting the symptoms.

Researchers are intensely looking for effective, noninvasive ways to prevent or slow down PD progression. Given the current results with neuroprotective candidates, it must be kept in mind that in addition of potential neuroprotection, other factors must be weighed before selecting agents for clinical trials. These include: the observed safety and tolerability of the compounds, the costs and accessibility of the proposed treatments, as well as how they compare to other candidates currently being tested in clinical trials (116). Only a systematic analysis of treatments will provide answers regarding efficacy, complications and limitations. In that context, oral treatments are especially attractive due to their potential to produce global effects, present lower risks compared to surgical interventions, and be less costly, which will allow for a higher impact in the population.

Although nobody can stop the path of time or change genetic background, it is becoming evident that there are certain actions that individuals can take to decrease the risk of developing PD. Supporting organic farming decreases exposure to pesticides in the food and also the environment. Regular exercise and a balanced diet with colorful fruits and vegetables supplemented with nuts may confer neuroprotection. Is this too simple or too obvious? The current raising rates of obesity and diabetes imply that these simple suggestions are not followed by many people, which increases their risk of all types of illness, not just PD (194). Interventions for cardiovascular disease include nutritional advice and recommendation of exercise programs. Perhaps, they should also be part of the prescription for the prevention and treatment of PD.

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**Abbreviations:** AD: Alzheimer's Disease, BDNF: Brain-derived growth factor, CALM PD: comparison of the agonist pramipexole versus levodopa on motor complications of PD, CIT: [123I]β-carbomethoxy-3-β-(4-iodophenyl)-tropene, CoQ10: Coenzyme Q10, DA: dopamine, DATATOP: Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism, EL: Encephalitis lethargica, GDNF: Glial-derived neurotrophic factor, HLA-DR: Human leukocyte antigen d-related, LRRK2: Leucine rich repeat kinase 2, LPS: Lipopolysaccharide, MAOB: monoamine oxidase B, MHC: Major histocompatibility complex, MPTP: 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridinium, nACh: Nicotinic acetylcholine, NGF: Nerve growth factor, NSAIDS: Nonsteroidal anti-inflammatory drugs, PD: Parkinson's Disease, PEP: Postencephalitic parkinsonism, PET: positron emission tomography, PPAR-gamma: Peroxisome Proliferator Activated Receptor-gamma, SNpc: Substantia Nigra pars compacta, SPECT: single photon emission computed tomography, T2DM: Type 2 diabetes mellitus, TH: Tyrosine hydroxylase, UPDRS: Unified Parkinson's Disease Rating Scale, UPS: Ubiquitin-proteasome system, UA: Uric Acid

**Key Words:** Parkinson's Disease, NSAIDS, Aging, Antioxidants, Pesticides, Neuroprotection, Alpha Synuclein, Review

## **Risk and prevention of Parkinson's disease**

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