

# An Improved Prevention and Treatment of Parkinson's Disease - A Review Considering Recent Findings in Genetics with Helpful Treatments

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## ABSTRACT

To properly prevent and treat Parkinson's disease (PD) and most other chronic diseases, the primary basis of the disease should be understood and also know how the genetic system operates which controls the disease. At present, we know that oxidative and nitrosative stress occurs in microglia in the substantia nigra (SN) in the midbrain which damages nearby dopaminergic neurons in the SN and its Nurr-1 DNA transcription factor/receptor. Nurr-1 is responsible for the production, storage, and transport or reuptake of dopamine. If Nurr-1 becomes defective or if there is a loss of dopamine production this is the basis for PD. The damage of the dopaminergic neurons occurs because microglia in the area generate a toxic peroxide called peroxynitrite (PN) which reacts with carbon dioxide producing peroxynitrite carbonate (PC), which is even more chemically reactive than PN. If the blood level of nucleoside or nucleotide purines is increased using inosine sustained release supplements, the urate product which is produced destroys PN and can prevent or control its or PC's damage. A variety of other non-toxic substances can be used to prevent the oxidative and nitrosative stresses, which cause the damage creating PD. However, recent discoveries indicate that the Nurr-1 mechanism can be stimulated using chloroquine and/or similar hydrophobic substances to produce more dopamine and also to protect against the mechanisms from the microglia which damage the neurons of the SN in the first place. Regardless of the initiating factors of PD, which are known to be virus, physical damage to the brain, or ingestion of certain chemicals which damage the dopaminergic neurons of the SN, it is possible to prevent the majority of PD or treating the disease to prevent the most debilitating form of this disease. Although this has not been clearly demonstrated in man yet, except for urate slowing the early course of the disease, it has been demonstrated in PD animal models. Since these treatments are essentially non-toxic, it is a matter of time before we can more completely control or prevent this disease. Since there are about one million cases in the USA and millions more around the world, we need to start the treatments which are outlined in this review. Furthermore, PD can be viewed as a model system for other neurodegenerative diseases.

**Key words:** Chloroquine, Inosine, Parkinson's disease, peroxynitrite, vitamin (sustained)

## HISTORY

Parkinson's disease (PD) was recognized by ancients from India who used the word Ayurveda, and in Sanskrit, it was termed Kampavata or tremor. In AD

175, Galen described the disease as palsy. However, in 1817, the English physician James Parkinson wrote an essay on "Shaking Palsy". Years later, a French physician described the disease by noting two major stages, namely tremor and rigidity. In the early 1960's, professor Arvid Carlsson first introduced L-DOPA or L- dihydroxyphenylalanine as

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the first effective treatment for the disease to correct the deficiency of the neurotransmitter dopamine to produce a normal state in patients with PD. Carlsson was a pioneer in neuropharmacology and was recognized as a corecipient of the Nobel prize for Medicine in 2000 [Figure 1].<sup>[1]</sup>

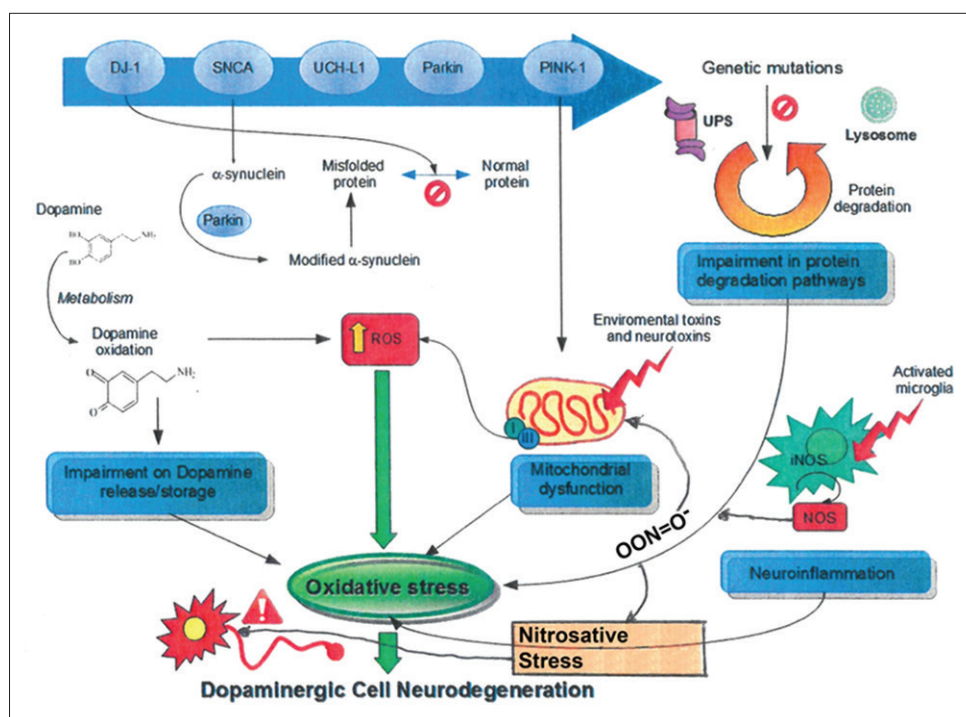
The deficiency of the neurotransmitter L-dopamine in the dopaminergic nerves of the substantia nigra (SN) in the midbrain is the basic cause of PD. Dopamine opposes acetylcholine and creates smooth movements of our extremities during body movements. The deficiency of dopamine creates this movement disorder and other deficiencies associated with the disease. In the later stages of the disease, many patients cannot talk, walk, or take care of the normal functions. PD resembles Alzheimer's disease in these patients. As we learn to treat neuroinflammatory degenerative diseases properly, we will realize that a proper treatment begins early with control of oxidative and nitrosative stresses.<sup>[2,3]</sup> We must treat these diseases in the early acute stage before the chronic stage makes them difficult to treat. As Ben Franklin so aptly put it, "An ounce of prevention is worth more than a pound of cure."

## CAUSES OF PD

PD is a disease which is caused by a variety of substances causing oxidative and nitrosative stress damage and eventually

death of dopaminergic neurons in the SN. The death of these neurons has been linked to viruses like the 1918 influenza epidemic with the H1N1 flu virus.<sup>[4]</sup> Many people developed PD later in life after having survived the flu. Another trigger for PD is physical damage to the brain through trauma caused by sports, accidents, or explosions associated with wars. A variety of different neurotoxic chemicals that can enter the blood-brain barrier (BBB) and activate glia and microglia can cause PD.<sup>[5]</sup> Particular pesticides which damage mitochondria and drugs like 6 hydroxydopamine and MPTP (1 methyl-4-phenyl-1,2,3,6 tetrahydropyridine) which is a precursor of the neurotoxin MPP<sup>+</sup> damage dopamine neurons...<sup>[6]</sup> The microglia cell in the brain is a type of macrophage which contains an enzyme named inducible nitric oxide (NO) synthase which can make a considerable amount of the gas NO (which contains a free electron).

NO then reacts with a similar amount of superoxide gas (oxygen with a free electron) generated from cell membranes using the enzyme NADPH oxidase. The two free radical gases react to produce peroxynitrite (OON=O<sup>-</sup>) which can then react with carbon dioxide producing a more highly active oxidant and nitrating compound peroxynitrite carbonate (PC).<sup>[7]</sup> PC can attack DNA, RNA, proteins, lipids, and mitochondria causing death of neurons, cells, and organelles. The level of peroxynitrite (PN) or its carbonate must be continuously controlled to control PD. None of the commercially available



**Figure 1:** Suggested damaging processes causing pathogenesis of Parkinson's disease (PD). Microglia become activated close to neurons and generate toxins like PN or PC which attack and kill dopaminergic neurons which contain the enzymes which produce dopamine. As these neurons die by various mechanisms including death of the mitochondria, production of dopamine decreases and eventually stops

drugs present on the market stop the PC caused oxidative stress from microglia and glia.<sup>[8]</sup> In addition, substances are needed to act as nitration or oxidation targets which degrade excessive PC once the two substances react together. Furthermore, because PC is continuously formed, the targets which react with PC must be generated in a similar kinetic manner as PC. Therefore, substances must be in sustained or time release form so that blood levels are continuously maintained over the course of action when excessive PN exists.

## ANTIOXIDANT SUBSTANCES USED TO LESSEN PN OR PC

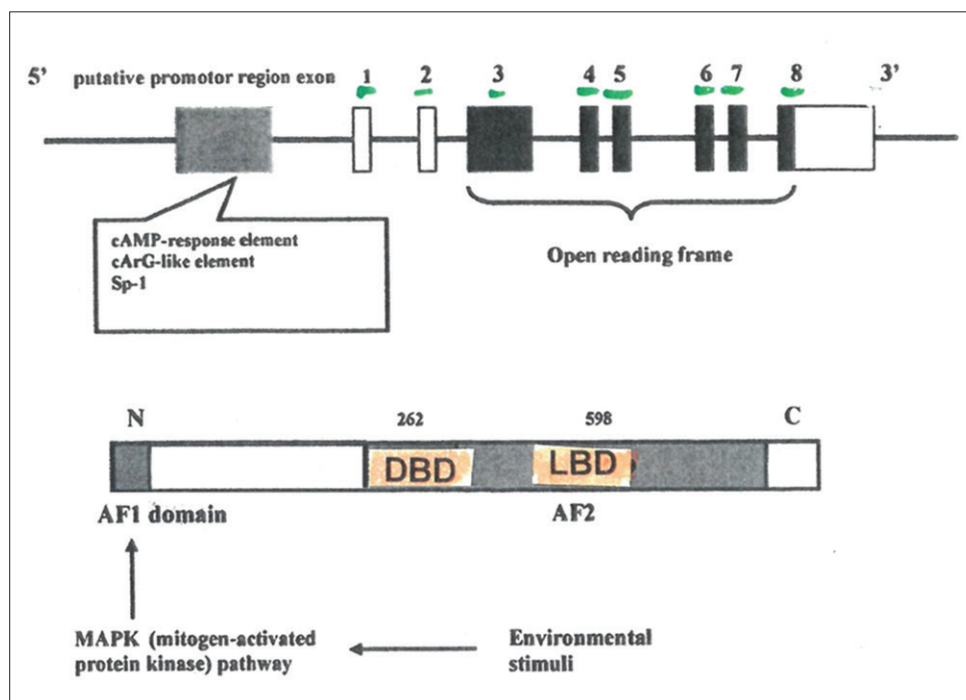
Substances known to lessen PN levels are as follows:

1. Ascorbic acid (Vitamin C) in sustained release form, and acetaminophen in sustained release form, acting 8 h - 650 mg tablets x2 every 8 h.<sup>[9]</sup>
2. Certain mono and diphenols, for example, cannabidiol in long lasting formula for the brain are targets of nitration of peroxynitrite.<sup>[10,11]</sup>
3. The pro-supplement inosine or other similar purine-like compounds which get into the brain and are bioconverted into urate, the salt of uric acid. Urate and PC react together causing destruction of PC. We hold the worldwide patent on this idea as well as the USA patent having been first to recognize this concept.<sup>[12-14]</sup>

We have produced a superior form of sustained release L-arginine and inosine which we used to treat sickle cell disease and crisis in children and found it quite effective. Schwarzschild had done a variety of clinical trials on the use of inosine to treat early PD patients and found that it actually slowed down the early progression of the disease in men but not in women.<sup>[14,15]</sup> This is the first clinical observation of its kind. The likely cause for the treatment failure in women is that a fixed dose of 3 g of inosine was used per female PD patient. In general, men have higher endogenous levels of urate in the blood. Three grams raised their blood urate high enough in men to get in the therapeutic range.

However, since the endogenous urate level in women is lower, 3 g inosine/day was insufficient to reach therapeutic levels of urate to slow early PD. PD is a neuroinflammatory degenerative disease mostly of older people.

This is important because as a person becomes advanced in age, the BBB often becomes leaky. If such an older person would take a drug, which should never enter the brain, i.e., it is crucial that the drug does not cross the BBB. However, if such a drug does cross the BBB in an older person, then such a person will be doomed to having an early death. Carbidopa (CA) is used in the USA and elsewhere, and in Europe, benserazide (BA) is used in combination with L-Dopa both normally do not cross the BBB in a younger person. However, if a person



**Figure 2:** The structure of the Nurr-1 gene which includes 8 exons. The open reading frame initiates in the third exon and terminates at the upstream region of the eighth exon that encodes 598 amino acids. Promotor region contains three elements - CRE, c-ArG, and Sp-1. B. Nurr-1 contains DBD (DNA binding domain) and LBD (ligand binding domain), Af1 domain is in the n-terminal region that can be activated by the MAOK pathway linked to environmental stimuli

is 65 years old or more, there is a more than reasonable chance that some of the so-called BBB impenetrable drugs will enter the brain.<sup>[16,17]</sup> Both CA and BA are drugs which are given with L-Dopa to Parkinson's patients who are generally older in age. Hinz and Cole<sup>[18]</sup> have published clear data that levodopa given to patients with PD from 1960 to about 1975 caused the death rate from PD to actually decline because L-Dopa is an effective drug for PD. However, when the FDA approved the combination of levodopa and carbidopa (1976) which is now used essentially only in combination today, the death rate has more than quadrupled over the next 40 odd years. Hinz and Cole has mentioned that CA reacts with Vitamin B6 (pyridinol-5' phosphate) forming a covalent Schiff base reaction complex which causes depletion of the active form of Vitamin B6 preventing hundreds of important transamination reactions in the brain and elsewhere creating an important nutritional deficiency. Hinz indicates that CA is the likely cause of the increased death rate. He demonstrates that the drug creates a nutritional collapse. He also believes that CA may be involved with the L-dopa created tachyphylaxis or dwindling effect of L-Dopa so that continuously higher doses of L-Dopa are necessary to maintain pharmacological effect.

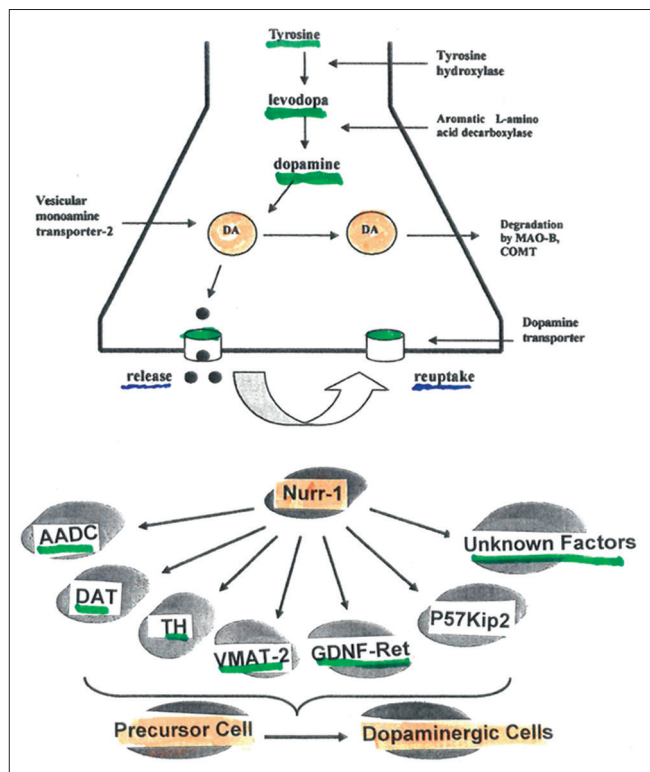
It is also highly likely that, in addition to the excellent data in the study of Hinz and associates, a leaky BBB in older patients allows CA or benserazide to enter the brain in Parkinson's patients which actually inhibits the formation of dopamine that accounts for the tachyphylaxis of L-Dopa and the increased death rate over time. This would occur because both drugs inhibit the decarboxylation of dihydroxyphenylalanine, and therefore, dopamine would not be easily produced. This would cause less dopamine to be produced in the dopaminergic neurons and cause tachyphylaxis and eventually death.

Since this increase in the death rate has occurred in over 40 years, it is surprising that the FDA and the manufacturers of these drug combinations were so unaware of these undeniable data. People who have been taking these drugs over the past 40 years are certainly victims of a governmental agency/drug companies that are not paying attention to the facts which are speaking loudly and clearly.

Nuclear receptor-related 1 protein (NURR1) also known as nuclear receptor subfamily 4, Group A, member 2 (NR4A2) is a protein that in humans is encoded by the NR4A2 gene.<sup>[19]</sup> NURR1 is a member of the nuclear receptor family of intracellular transcription factors. NURR1 plays a key important role in the growth and maintenance of the dopaminergic system of the brain [Figures 2 and 3].

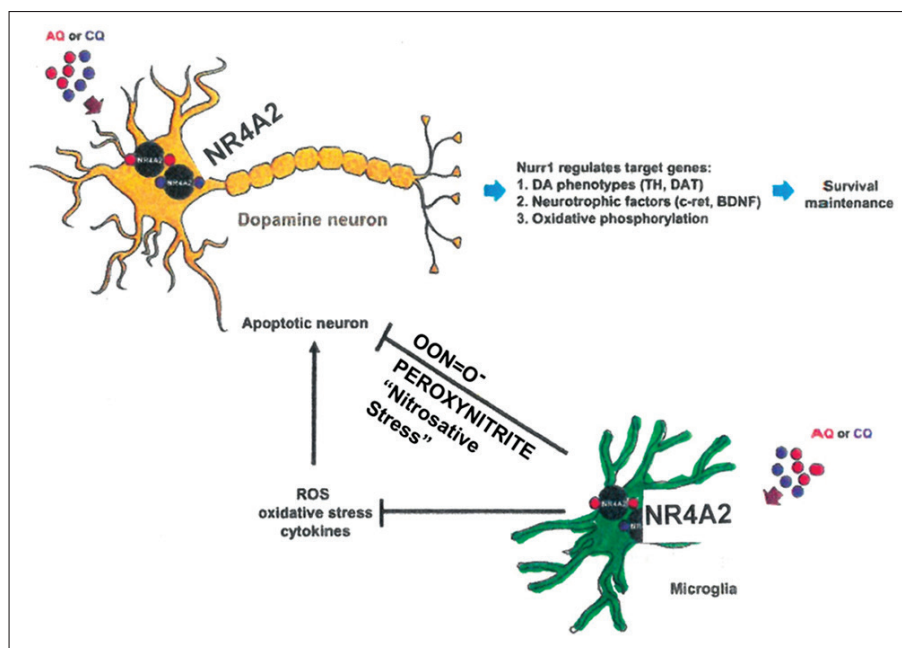
## NURR-1 AND INFLAMMATION IN THE CENTRAL NERVOUS SYSTEM (CNS)

Inflammation in the CNS often results in the activation of macrophage-like microglia, which can generate a considerable amount of PC. Normally, PC is the killing mechanism used to protect us against a variety of different infections. Since nuclear factor kappa b can be induced by physical damage, viruses, a diverse group of chemicals like pesticides and environmental pollutants induced causing inflammation via peroxynitrite carbonate (PC)-these are the fundamental basis of PD.. The inflammatory system produces peroxynitrite (PN), PC, nitric oxide, superoxide, various interleukins, tumor necrosis factor etc. These ultimately damage the Nurr-1 mechanism. In order to operate properly and produce dopamine, Nurr-1 needs cooperation and stimulation from other factors to participate in its production, storage and release of dopamine. Nurr-1 needs to be sumoylated, and its coregulator glycogen synthase kinase 3 needs to be phosphorylated for these inflammatory reactions to occur. Sumoylated Nurr-1 recruits CoREST, a complex composed of multiple proteins that are similar to chromatin modifying enzymes. The Nurr-1/CoRest complex inhibits the transcription of inflammatory genes. Therefore, this gene complex actually represses inflammation and its



**Figure 3:** Nurr-1 regulates the expression of a variety of components that produce and control dopamine production and distribution. Like AADC, DAT, TH, VMAT-2 Ret, and P57-Kip2. A. Depicts the synthesis of dopamine. TH and AADC are crucial enzymes for synthesis of dopamine, VMAT-2=Dopamine storage, DAT=dopamine reuptake, B. NURR-1 factors in dopamine neurons: AADC.dat, GDNF-RET, P57KIP2, VMAT-2, and unknown factors





**Figure 4:** Dopaminergic neurons close to activated microglia generating peroxynitrite and damaging through oxidative and nitrosative stress on the neuron creating apoptosis

damaging products. Under the correct circumstances, Nurr-1 and its product dopamine production, storage, and transport are actually quite protective of the dopamine system by turning off damaging mechanisms in the activated microglia [Figure 4].<sup>[20-22]</sup>

### Function of nurr-1 structure

It has been found that Nurr-1 DNA transcription factor/receptor does not have a discrete binding cavity but contains a patch filled with hydrophobic amino acid side chains from non-polar amino acid residues of Nurr-1's coregulators such as SMRT and NCoR, which bind to this hydrophobic patch [Figure 5].<sup>[23,24]</sup>

Analysis of Nurr-1 tertiary structure has shown that the binding surface of the ligand binding domain (LBD) is located between the 11<sup>th</sup> and 12<sup>th</sup> alpha helices. This study also found essential structural components of the hydrophobic patch, the three amino acid residues, F574, F592, and L=593; mutation of any of the three inhibits the LBD activity.<sup>[25,26]</sup> By combining the substances that control oxidative/nitrosative stresses and stimulating Nurr-1 with non-toxic agonists, PD can likely be prevented and/or controlled if treated early enough, so reversibility of the disease is possible. Diabetes is a similar oxidative and nitrosative stress type of disease and control of O/N stress, and using simple substances that control blood glucose or excessive calories produces similar healthy responses.<sup>[26]</sup> In the case of PD, it is necessary to control O/N stress using antioxidants and inosine and gives Nurr-1 stimulants and



**Figure 5:** Nurr-1 DNA transcription factor binding to DNA. If chloroquine is present, it binds to greasy spot (ligand binding domain) on Nurr-1 and stimulates production, storage, and release of dopamine. Chloroquine helps protect against microglia attack on Nurr-1 and protects against formation of Parkinson's conditions

the correct oral precursors to produce dopamine either L-tyrosine or L-Dopa.

### To effectively treat PD early and continuously, PN production must be controlled

1. We must protect the dopaminergic neurons from oxidative and nitrosative stresses. We could give orally sustained release antioxidants - Vitamin C, 2-4 g/day in divided doses. Even higher doses are well tolerated by most people.

2. Give 3–5 g of sustained release orally of inosine per day in divided doses every 12 h. In case of minor side effects, reduce dose but side effects can be easily controlled with a smooth teaspoonful of sodium bicarbonate dissolved in water and taken orally several times/day.
3. Use orally sustained release L-arginine at 3 g every 12 h. This increases the production of the amounts of NO in the blood vessels and lowers PN or PC production by producing an imbalance between the equivalent amounts of superoxide compared to available amounts of NO through feedback regulation.
4. Use oral SR acetaminophen. Tylenol arthritis formula - 2–650 mg every 8 h. This is to be sustained every day until treatment is ended.
5. Use oral cannabidiol - 500–1000 mg/day.
6. Use glutathione or glutathione precursors like N-acetyl cysteine (NAC Sustain 600 mg) orally at 1x or 2x/day or similar doses of NAC derivatives, for example, N-acetyl ethyl ester (sustained release).
7. Dopamine must be maintained continuously without damaging protective mechanisms for Nurr-1. This requires the use of sustained release L-tyrosine 500 mg - 2–3 times/day which contains Vitamin B6 sustained release. L-tyrosine could be replaced by sufficient amounts of L-Dopa as needed to maintain correct movements and decrease side effects.
8. Nurr-1 agonists or stimulators should be given or maintained so that dopamine production is stimulated. NURR-1 is the receptor/DNA transcription factor responsible for the production of tyrosine hydroxylase, amino acid decarboxylase, and dopamine transporter in the SN dopaminergic neurons. Dopamine is known to be stimulated by chloroquine, amodiaquine, and various derivatives of these substances. These doses in humans for PD would be likely be best determined through clinical trials. Chloroquine dosing for malaria is to give orally 1 g for the 1<sup>st</sup> day of therapy and 500 mg for 6–8 h the same day. The 2<sup>nd</sup> day and the 3<sup>rd</sup> day also give orally 500 mg chloroquine which is full dosing for a week.
9. It is likely that chloroquine dosing for PD would be 250 mg chloroquine every other or possibly on the 3<sup>rd</sup> day for several weeks with the dose tapering after the initial time, but dosing in man for chloroquine treatment for PD has not been optimized. We know that chloroquine has a long half-life of a week or more, so dosing for chloroquine would likely be in smaller doses stretched out for a much more prolonged period of time relative to dosing for malaria. We must give a variety of standard doses of 500–1000 mg of L-amino acids orally to replace depleted L-amino acids such as l-tyrosine, L-tryptophan, and 5 hydroxytryptophan. The best dosing would need to be found experimentally for individuals.
10. L-Dopa sustained release could be used orally with or without L-tyrosine since the body converts either substance into dopamine. Either substance could be

given orally at the correct doses (500 mg) or more several times per day, depending on orders from the attending physician. It should be used at doses that alleviate the patients' symptoms but does not produce major side effects. Possibly using L-tyrosine as the precursor for the production of dopamine would produce less side effects.

11. Use oral and sustained release L-arginine at doses of 3 g every 12 h. This produces extra and continuous amounts of NO and upsets the ratio between available superoxide and NO. If there is extra NO available, this creates a feedback inhibition of the production of PN or its carbonate. This creates a *de facto* inhibition of excessive peroxynitrite production which is protective for dopaminergic neurons which helps to prevent PD.

## CONCLUSIONS

Recent research indicates that, using multiple supplements, we can control or prevent early PD caused by oxidative and nitrosative stress from PN. In addition, if we add the stimulation of dopamine production and the protection from continuous damage which occurs due to dopaminergic neurons by giving continuous chloroquine which binds to the Nurr-1 DNA transcription factor/receptor, the control of chronic disease state is at hand. This is clearly indicated by animal experimentation using a 6 hydroxydopamine study even without control of oxidative and nitrosative stress.

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