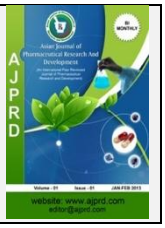
Available online on 15.10.2023 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

Parkinson Disease: A Review

Annu Kumari*, Muskan Gupta, Gaurav Rankawat, Abhishek Rankawat

Department of pharmacy, Arya College of Pharmacy, Jaipur, Rajasthan, India

A B S T R A C T

Parkinson disease is a neurodegenerative progressive disorder which caused due to increase level of Ach and lack of dopamine inside the brain. The dopaminergic cell death were found inside the brain in case of Parkinson disease. It's a type of motor deficiency disease. Many symptoms like bradykinesia, tremor, postural instability, loss of sense of smell etc. are arises in Parkinson disease and there is no specific cure for Parkinson. A molecular biomarker is important to find because it differentiate the Parkinson from other disease and this disease mainly consultant by the neurologist. The management and treatment of Parkinson disease is based on some drugs, like levodopa, dopamine agonist, MAO-beta inhibitor, CoMT inhibitors and many more. They are used with or without in combination and Parkinson include various risk factor like herbicides, pesticides, metal exposure etc. Various type of surgical approaches. Deep brain stimulation are good for Parkinson patients. Nicotine, caffeine, hormone replacement therapy are the some protective factors which overcome the chances of Parkinson disease.

Key words: Parkinson Disease, Progressive, Hypocretin

A R T I C L E I N F O: Received 15 May 2023; Review Complete 19 Aug. 2023; Accepted 24 Sept. 2023; Available online 15 Oct. 2023

Cite this article as:

Kumari A, Gupta M, Rankawat G, Rankawat A, Parkinson Disease: A Review, Asian Journal of Pharmaceutical Research and Development. 2023; 11(5):35-40. DOI: http://dx.doi.org/10.22270/ajprd.v11i5.1318

*Address for Correspondence:
Annu Kumari, Department of pharmacy, Arya College of Pharmacy, Jaipur, Rajasthan, India

INTRODUCTION

Parkinson disease is a type of neurogenerative chronic disorder or motor disorder shows the lack of dopamine in basal ganglia. It show some symptoms like bradykinesia, rigidity and disorder, excessive movements of limb, constipation. Parkinson disease is found in approx. 1%of population above the age of 60. It mainly found due to imbalance between inhibiting dopamine and excitatory Ach and it is related with the lack of dopaminergic neurons in substantia nigra and the abnormal deposits of protein (alpha-synucein in brain) it is considered in idiopathic, only 10% cause are mostly discern in young people. This disorder is progressive, it can show their effect on quality of life. Diagnosis is based on patient medical history, symptoms and physical examinations. In some doubtful cases the SPECT scans are performed. Some other scans can be performed. It shows minor symptoms on stage 1 but show major serious effects on stage 5. After the introduction we will discuss about pathogenesis, side effect, diagnosis, risk factor and diagnosis. Diagnosis of Parkinson disease is important to identify the initial feature with sign and symptoms which suggest the other cause of Parkinson disease[1,2,3].

History

Major turning point in Parkinson disease involves the identification of lewy bodies as pathological insignia (hallmarks) in 1912 by Frederick lewy and also discovered the deficiency of dopamine and its action in Parkinson animal model. Oleh harnykiewicz and arvid carlsson started their research in 1957. They established the relation between deficiency of dopamine and Parkinson disease. In 1967 the high levodopa dosage therapy is introduced by George cotzias [4]. The insignia of neurodegenerative disease is a type of neuronal loss. The braak and co-workers introduce a scheme for Parkinson which is established on distribution of alpha synucein. Day by day when disease progress then dopaminergic neurons and locus cerulleus neurons are effected after that the last stage, some areas like lobe structure, medial temporal and convexity cortical areas are affected due to extends in pathology. In San Francisco bay area William Langston (a neurologist) show seven patient in 1982 who were using the synthetic heroin [5]. The other

features are formed in Parkinson disease when rigidity and bradykinesia are combined. In chromosome 4_q21-$_q23$ the genetic markers are fund by colleagues and polymer polos in 1996 which is directly linked with the Parkinson phenotype [6,7]. Some other autonomic symptoms are found in Parkinson disease like constipation, urinary retention, difficulty in swallowing and these do not improve after the treatment. Demensia and depression are very common in this disease. Grait disorder is a medical condition which is not found earlier in Parkinson disease but it is easy to understand.

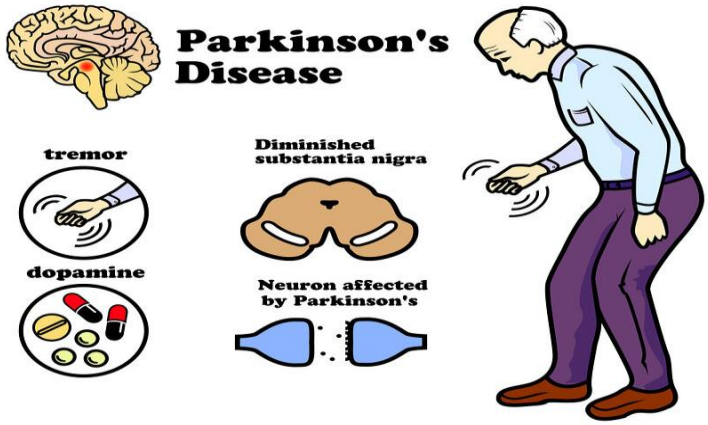


Figure :1

Pathogenesis

In New Jersey area various people of Italian family were identified as having Parkinson disease [8]. The first cause is found due to the accumulation of alpha- synuclein in brain and firstly the substania niqra, mainly degenerative and after that the dopamine loss in basal ganglia which control movement. The insignia of Parkinson disease is loss of cell within substania nigra which particularly affect the para compacta on death time on comparison with unaffected this site of brain lost 50-70% of its neuron [9].

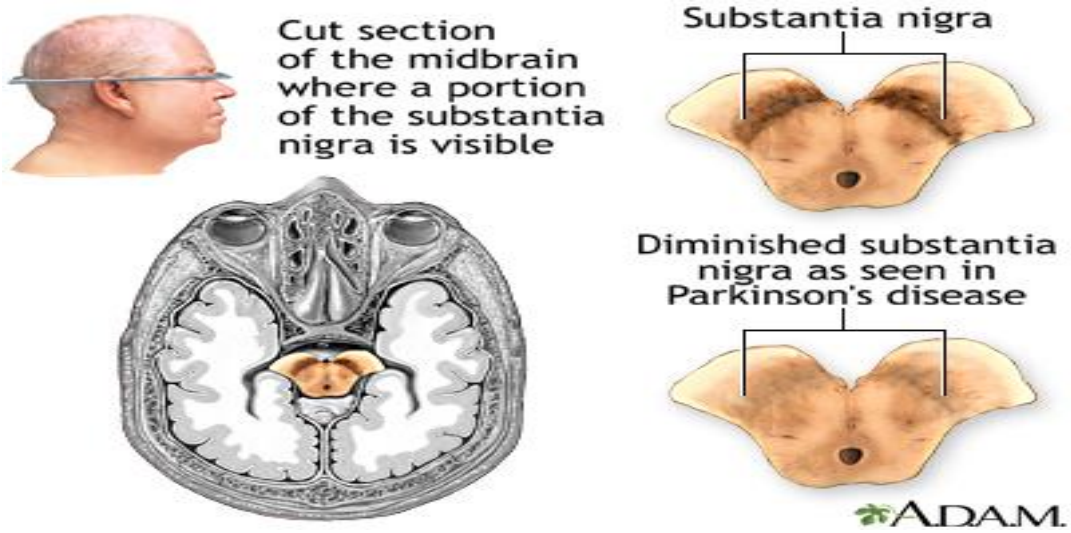


Figure 2

In medulla oblongata the initial pathological changes are observed it can divide into several stashes so in initial stage mean in braak stage 1and 2 pre symptomatic patients are found and as time increases the disease become advanced so in braak stage 3 and 4 various parts like midbrain, basal forebrain, substantia nigra etc. are involved. At last the changes appeared in neocortex (cover half the volume of human brain). These pathological changes are depend on the distribution of the lewy bodies lewy bodies is the deposition of protein (alpha-synuclein) in brain. It included a type of protein (heat shock) which is responsible to target the other protein for breakdown. Parkin protein developed the lewy bodies so the mutation in parkin protein show Parkinson syndrome. Mostly lewy bodies are scene in dementia and Parkinson disease but these are not a hall mark for any other neurodegenerative disease[10]. In initial Parkinson disease the LB are deposited firstly on the site of olfactory bulb. The initial clinical features (like disturbance is taste and smell) increased the possibility of formation of LB which may be activate the pathway who mainly show the neuronal dysfunction.

Neurochemical Biomarkers / Molecular Markers

HYPOCRETIN

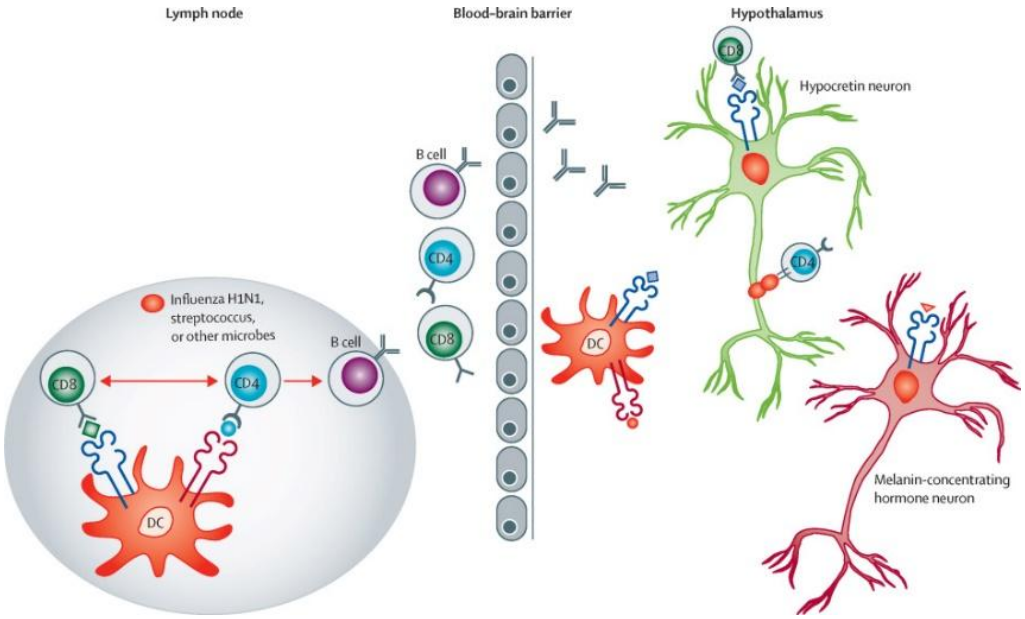


Figure 3

Hypocretin is a neuropeptide hormone which is also expressed as orexin. Hypocretin is secreted by the neurons which is present in hypothalamus hormone like heart rate, sleep wake cycle. Cardiovascular responses and hypertension[11,12]. If the number of Hypocretin decreases in hypothalamus then it may cause the narcolepsy condition in Parkinson disease patients. The amount of Hypocretin is directly to the disease that means low concentration of Hypocretin produce high rise of disease in Parkinson disease patients. The concentration of Hypocretin is found in low amount in Parkinson disease patients as compared to healthy patients[13]. The level of GFAP (glial fibrillary acidic protein) arises in the Parkinson disease patient in cerebrospinal fluid[13]. Some condition of GFAP like hypo phosphorylation frequently found in Parkinson patients and these variation in astrocytes are directly linked with pathogenesis of Parkinson disease. Astrocytes are also responsible for the incensement of Parkinson disease because they produce the proinflammatory cytokinesis which damage the dopaminergic neurons[14,15].

DOPAMINE

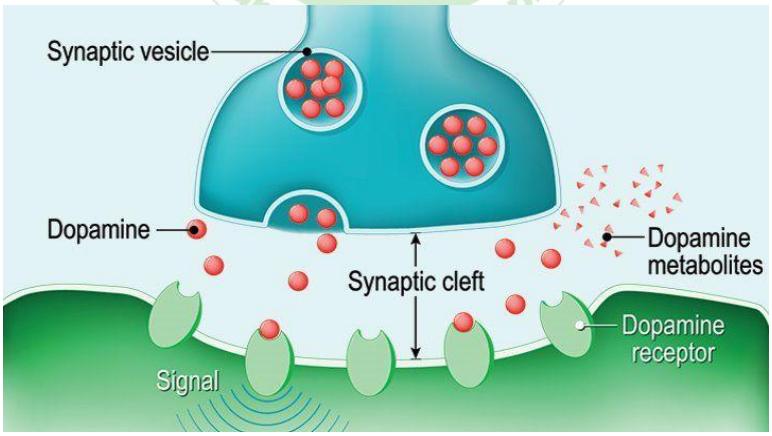


Figure 4

Dopamine is part of catecholamine neurotransmitter which is secreted from the SN and other parts of brain. TH formed the L-dopa which is further converted into dopamine. The level of dopamine is reduced when the dopaminergic neurons are loss[16]. The level of dopa is control by the dopamine transporter and the dopamine is reuptake from synapses and its store with dopamine transporter system. The excess amount of dopamine stored in vesicle by the help of vesicular monoamine transporter 2 because free dopamine produce the toxicity for neurons. If the level of dopamine or DAT is changed then it may show the indication of Parkinson disease. There is six types of receptor which activated by dopamine D_1R, D_2R, D_3R, D_4R, D_55 and the high risk of PD shown. When the level of D_3R receptor decreases so its also considered as biomarker for PD[17,18].

Neuroimaging biomarkers- now a days our technology are modified so they have ability to detect the brain abnormalities on those patients who suffer from PD by the

help of various techniques like TCS (transcranial B mode sonography) , SWL (susceptibility weighted imaging), DWL (diffusion weighted imaging), PET scan (positron emission tomography), SPECT scan (single photon emission computed tomography)[19].

SYMPTOMS

MOTOR

- Bradycardia
- Walking difficulty
- Tremor, postural instability
- Olfactory dysfunction
- Constipation

NON MOTOR

- Excess salivation
- Mental issue
- Sense of smell
- Autonomic dysfunction
- Sleep disorder

Figure 5

RISK FACTOR/ ETIOLOGY

Use of herbicides, work near the industrial plants and pesticides are the causes of PD. Dopaminergic cell death due to environmental toxin so it's a major cause of PD. Aggregation of heavy mental in substantia nigra also a cause of PD[20]. Cytochrome P4502D6 is an enzyme which is responsible for the development of PD. Aggregation of heavy metal in substantia nigra also a cause of PD. Cytochrome P4502D6 is an enzyme which is responsible for the development of PD[21]. According to two neurologist, influenza infection is the major cause of PD but according to other studies, influenza infection cannot developed or increase the chances of PD[22]. Family history is also a risk of PD in 1950, it was recognised that the pigmented neurons ae dopaminergic in nature that are lost in SN and alpha synuclein alter its function then it play a major role in etiology of PD[23,24]. Many risk factor included like agriculture occupation, metal exposure, traumatic head injury and many more.

TREATMENT AND MANAGEMNET

There is no cure of Parkinson disease available till date but many drug and therapies for preventing its symptoms are available now. The administration of drug for the treatment of Parkinson disease are based on the symptoms which arises in patient. There are very medications are available on the basis of motor and non-motorsymptoms[25].

DRUGS: these drugs increases the level of dopamine in SN. These medication improve the PD patient condition by increasing dopamine level. These drugs act on dopamine receptor and mimic the action of dopamine.

LEVODOPA: Levodopa is a metabolic precursor which show the high effect. Levodopa is converted into dopamine with the help of dopa decarboxylase in dopaminergic neurons. When we orally administration the levodopa then it can be approx. to 70% decarboxylated in gut system before reaching the CNS part. It mean it show less effect in CNS. Carbidopa is drug which is peripheral inhibitors of dopa decarboxylase but it cannot pass through BBB. So in the market, levodopa and carbidopa are available in combination. By this combination levodopa in the presence of carbidopa can reaches the CNS easily and used as dopamine precursor. Levodopa also show side effect like dizziness, nausea, vomiting, headache, insomnia[26].

CLASS OF DOPAMINE AGONIST: Dopamine agonist are available on the basis of two classes' ergot and non-ergot drugs. The ergot drugs are cabegoline, bromocriptine, lisuride and pergolide and the no ergot drugs are mainly ropinirole and pramipexole. These drugs bind with dopaminergic post synaptic receptors by which the receptor

stimulate. They used first to delay side effects which is produced by levodopa and carbidopa like dyskinesia. But dopamine agonist cannot be early introduced because it show slow recovery of disease. When the symptoms of PD are not controlled by other drugs like levodopa then the dopamine agonist can used as a monotherapy. It show some side effects like hallucination, orthostatic hypotension, leg oedema and a major side effect impulse control disorder (ICD)[27].

MAO-B INHIBITORS: MAO-B inhibitors include some drugs like rasagiline, selegiline, safinamide these drugs are also used in PD to manage the symptoms. These drugs are not administered with combination in early stages or may be used with other therapies or treatment. MAO-B inhibitors reduce the symptoms like motor fluctuations. MAO-B and MAO-A both are found in cell. MAO-A in intestine and MAO-B in brain. They are a type of enzyme which break down the dopamine on inside so that the MAO-B inhibitor drug can prevent or block the action of this enzymes. These types of drugs can provide to reduce the symptoms but there are various possible side effect of this inhibitor like nausea, insomnia, headache, confusion, agitation.

COMT-INHIBITORS: COMT Include entacapone, talcapone, opicapone. They reduced the symptoms of PD but also show some side effects like dyskinesase, dizziness, nausea, vomiting, dry mouth etc. these drugs are inhibit the action of COMT (catechol-o-methy trasferase). They prevent the conversion of methylated levodopa from the levodopa COMT is anenzyme which breakdown the dopamine neurotransmitter inside the brain so these drugs can inhibit or block the action of this COMT enzyme. The primary role of this drug to prolong the action of levodopa they are well tolerated drugs.

CONSULTATIONS: neurosurgeon, gastroenterologist, physical therapist, psychiatrist, speech therapist, urologist, dietitian, otolaryngologist.

PROTECTIVE FACTORS

Hormone replacement therapy, nicotine, NSAIDs, omega 3 fatty acid, smoking, caffeine[28,29]. Consumption of caffeine reduce the risk of PD at age of 65 years and above. Omega 3 fatty acid prevent the cell degeneration and there supplements help to control the genes which cause the problem like brain inflammation. Hormone replacement therapy reduce some symptoms which are produced by PD. Nicotine has neuroprotective ability, which is useful for both treatment and prevention of PD. Nicotine interact with CNS dopaminergic system by which it protect against the neurodegenerative but smoking is not considered in protective factor because it produce various serious disease like lung cancer, CVS etc.

REFERENCE

1. Mirpour S,Turkbey EB,Marashdeh W,El Khouli R,Subramaniam RM, Impact of DAT-SPECT on Management of Patients Suspected of Parkinsonism. Clinical nuclear medicine. 2018 Oct
2. Alexoudi A,Alexoudi I,Gatzonis S, Parkinson's disease pathogenesis, evolution and alternative pathways: A review. Revue neurologique. 2018 Dec
3. Kabra A,Sharma R,Kabra R,Baghel US, Emerging and Alternative Therapies For Parkinson Disease: An Updated Review. Current pharmaceutical design. 2018
4. FahnS . The 200-year journey of Parkinson disease: reflecting on the past and looking towards the future. Parkinsonism RelatDisord 2018;46:S1–5.doi:10.1016/j.parkreldis.2017.07.020
5. Langston JW . The MPTP story. J Parkinsons Dis 2017;7:S11–19.doi:10.3233/JPD-179006 G
6. Polymeropoulos MH et al . Mutation in the -synuclein gene identified in families with Parkinson's disease. Science 1997;276:2045–7
7. GolbeLI , Di Iorio G , Sanges G , et al . Clinical genetic analysis of Parkinson's disease in the Contursi kindred. Ann Neurol 1996;40:767–75.
8. GrattonC,KollerJM,ShannonW,GreeneDJ,SnyderAZ,PetersenSE,PerlmutterJS,Campbell MC, Emergent Functional Network Effects in Parkinson Disease. Cerebral cortex (New York, N.Y. : 1991). 2018 Jun 6
9. Braak H, Bohl JR, Müller CM, et al. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered, MovDisord, 2006, vol. 21 (pg. 2042-2051)
10. Chung KK, Zhang Y, Lim KL, et al. Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease, Nat Med, 2001, vol. 7 (pg. 1144-1150)
11. Hagan, J. J., Leslie, R. A., Patel, S., Evans, M. L., Wattam, T. A., Holmes, S., et al. (1999). Orexin a activates locus coeruleus cell firing and increases arousal in the rat. Proc. Nat. Acad. Sci. U.S.A. 96, 10911–10916. doi: 10.1073/pnas.96.19.10911
12. Imperatore, R., Palomba, L., and Cristino, L. (2017). Role of Orexin-a in hypertension and obesity. Curr. Hypertens. Rep. 19:34. doi: 10.1007/s11906-017-0729-y
13. Takahashi, Y., Kanbayashi, T., Hoshikawa, M., Imanishi, A., Sagawa, Y., Tsutsui, K., et al. (2015). Relationship of orexin (hypocretin) system and astrocyte activation in Parkinson's disease with hypersomnolence. Sleep Biol. Rhythms 13, 252–260. doi: 10.1111/sbr.12112
14. Clairembault, T., Kamphuis, W., Leclair-Visonneau, L., Rolli-Derkinderen, M., Coron, E., Neunlist, M., et al. (2014). Enteric GFAP expression and phosphorylation in Parkinson's disease. J. Neurochem. 130, 805–815. doi: 10.1111/jnc.12742
15. Rappold, P. M., and Tieu, K. (2010). Astrocytes and therapeutics for Parkinson's disease. Neurotherapeutics 7, 413–423. doi: 10.1016/j.nurt.2010.07.001
16. Obeso, J. A., Rodríguez-Oroz, M. C., Benitez-Temino, B., Blesa, F. J., Guridi, J., Marin, C., et al. (2008). Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. Mov. Disord. 23, 548–559. doi: 10.1002/mds.22062
17. Nagai, Y., Ueno, S., Saeki, Y., Soga, F., Hirano, M., and Yanagihara, T. (1996). Decrease of the D3 dopamine receptor mRNA expression in lymphocytes from patients with Parkinson's disease. Neurology 46, 791–795. doi: 10.1212/WNL.46.3.791
18. Caronti, B., Antonini, G., Calderaro, C., Ruggieri, S., Palladini, G., Pontieri, F. E., et al. (2001). Dopamine transporter immunoreactivity in peripheral blood lymphocytes in Parkinson's disease. Neural. Transm. 108, 803–807. doi: 10.1007/s007020170030
19. Chung, E. J., Kim, E. G., Bae, J. S., Eun, C. K., Lee, K. S., and Oh, M. (2009). Usefulness of diffusion-weighted MRI for differentiation between Parkinson's disease and Parkinson variant of multiple system atrophy. J. Mov. Disord. 2, 64–68. doi: 10.14802/jmd.09017
20. Burke, W. J. (2003). 3,4-dihydroxyphenylacetaldehyde: a potential target for neuroprotective therapy in Parkinson's disease. Curr. Drug Targets CNS Neurol. Disord. 2, 143–148. doi: 10.2174/1568007033482913
21. Elbaz, A., and Tranchant, C. (2007). Epidemiologic studies of environmental exposures in Parkinson's disease. Neurol. Sci. 262, 37–44. doi: 10.1016/j.jns.2007.06.024
22. Estupinan, D., Nathoo, S., and Okun, M. S. (2013). The demise of Poskanzer and Schwab's influenza theory on the pathogenesis of Parkinson's disease. Parkinsons Dis. 2013:167843. doi: 10.1155/2013/167843
23. Ehgoetz Martens KA,ShineJM,WaltonCC,GeorgiadesMJ,GilatM,HallJM,MullerAJ,SzetoJYY,Lewis SJG, Evidence for subtypes of freezing of gait in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2018 Jul
24. Chung SJ,YooHS,LeeHS,OhJS,KimJS,SohnYH,Lee PH, The Pattern of Striatal Dopamine Depletion as a Prognostic Marker in De Novo Parkinson Disease. Clinical nuclear medicine. 2018 Aug 27
25. Lauretani, F., Saginario, A., Ceda, G. P., Galuppo, L., Ruffini, L., Nardelli, A., et al. Treatment of the motor and non-motor symptoms in

Parkinson's disease according to cluster symptoms presentation. Curr. Drug Targets 2014; 15:943–947
26. Goldenberg, M. M. (2008). Medical management of Parkinson's disease. P T 33, 590–606.
27. Lees AJ, Stern GM. Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease, J Neurol Neurosurg Psychiatry, 1981; 44:1020-1023
28. AscherioA , Schwarzschild MA . The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016; 15:1257–72.
29. Breckenridge CB , Berry C , Chang ET , et al . Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis. PLoS One 2016;11:e0151841.