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Review Article

Parkinson's disease pathogeny and treatments: A narrative review

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Abstract

Parkinson's disease is a multifaceted illness that requires interdisciplinary approach to be fully addressed. The etiology of the disease is not completely understood, but genetic and environmental cues play important roles. Histological hallmarks of the disease are the accumulation of alpha-synuclein aggregates, mitochondrial changes and loss of dopaminergic neurons in the substantia nigra. The dopaminergic shortage leads to many motor and non-motor symptoms that affect patient quality of life. Current treatments are symptomatic only, for none can stop disease progression or cure it. Among them are intense physical exercise, dopaminergic drug intake, deep brain stimulation and the use of medical cannabis. Dopaminergic drugs help increase the levels of dopamine in the synaptic cleft or stimulate dopamine receptors directly. Intense physical exercise has been proved beneficial and safe. Deep brain stimulation is done by surgically implanting electrodes and has shown immediate improvements. Medical cannabis is being used mostly to fight non-motor symptoms, such as pain, anxiety, appetite loss and depression. Exciting researches are being done with stem cells, animal models and wearable technology, which might answer many current doubts, but finding early markers to detect and stop the disease progression remains a challenge.

Keywords: Parkinson disease, Deep brain stimulation, Physical exercise, Medical cannabis, Dopaminergic drugs, Dopaminergic circuitry, Substantia nigra, Nigrostriatal dopaminergic circuitry, Stem cells, Dementia

Introduction

Parkinsonism is a syndrome characterized by dysfunction of specific brain circuitry. The clinical condition of each patient characterizes one among the many forms of the syndrome: post-encephalic, drug related, vascular, just to name a few examples. The presence of one such cause leading to the development of parkinsonian symptoms is present in secondary parkinsonism, and its different clinical developments help guide diagnose and treatment [1,2]. The most common presentation of parkinsonism, however, is its idiopathic and age-related form, called Parkinson's disease (PD). The neural dysfunction typical of this clinical entity is caused by neurotransmitter deficiency and death of neurons, which triggers neurological signs that ultimately impairs patients' quality of life [3,4].

PD affects millions of people worldwide and is the second most prevalent neurodegenerative condition, next to Alzheimer disease, and has chronic, continuous, and disabling nature. There are several treatment options, but none capable of stopping or reversing the disease's progression. Diagnosis is still also a hindrance, for there is no molecular marker exam to perform *in vivo*. Therefore, PD keeps posing challenges to the scientific community, in many fields and fronts.

History of PD

Its first description is from 1817, on the monograph "An Essay on the Shaking Palsy", by British physician James Parkinson [3,4]. He described his subjects' resting tremor, shuffling gait, stooped posture, sleep problems, and constipation. He also noted the degenerative nature of the disease, with its ever-growing disability, and called it paralysis agitans. A few years later, bradykinesia and

rigidity were added to the list of symptoms [3,4], and the syndrome was renamed PD, in honor of its first describer. Thereafter, many more studies described motor and non-motor features (Table 1), and detailed neuropathological, neurochemical, neurophysiological, and neuroimaging characteristics of PD [5]. Favorable treatment results were first achieved in the 1950s with levodopa, a dopamine (DA) precursor which, when paired with carbidopa (Figure 1), became the mainstay of medical therapy and remains so to this day [6,7].

Continuous advances have been made regarding the physiologic mechanisms and genetic causes of PD, and additional treatment options were developed [13,14]. DA agonists, monoamine oxidase type B inhibitors and catechol-O-methyltransferase inhibitors have been added to the pharmacological arsenal. But even the rise of new pharmacological options is insufficient, and the prevalence of patients, either harmed by persistent symptoms or afflicted by severe side effects of the medication, has pressed scientists towards

Table 1: Examples of motor and non-motor symptoms of PD [3,35,39,134,135].

Motor-symptoms	
Bradykinesia	Impairment of voluntary movements that afflicts arms, hands, face and legs.
Hypokinesia	Decrease in body movement.
Akinesia	Loss of movement, like loss of arm swing.
Freezing	Sudden but temporary inability to move; a stiff feeling in arms, legs, and torso area, such as walking or getting up from a chair.
Resting tremor	It is the classic rhythmic tremor of PD. Initially starts in one hand, foot or leg of one side of the body and eventually hits both sides. It can also occur in the jaw, chin, mouth, or tongue and provoke a feeling of internal tremor. It does not directly cause muscle force loss.
Postural instability	Trouble maintaining balance.
Rigidity	Stiffness or inflexibility of muscles.
Non-motor symptom	
Sleep abnormalities	Ex: moving while in REM sleep, insomnia, daytime sleepiness.
Depression	Mood disorder that involves a persistent feeling of sadness and loss of interest.
Cognition problems	Difficulty in learning new material, problem solving, memory and concentration, disorientation and confusion.
Autonomic dysfunction	Orthostatic hypotension, constipation, fecal incontinence, bladder disturbances, olfactory dysfunction, sweating and sexual dysfunction.
Mood changes	Irritability, impatience, aggression.
Hallucinations	Hearing or seeing things others do not.
Dementia	Common neurodegenerative condition that presents itself with a wide range of neuropsychiatric, cognitive, sleep, motor, and autonomic symptoms.
Paranoia	Feeling suspicious or distrustful of others.
Weight Loss	Accompanied by appetite loss, weight loss is more likely in later phases of the disease and could lead to malnutrition or exacerbate motor and non-motor symptoms.
Delusions	False, unrealistic or strange beliefs.
Anosmia	Lack of the senses of taste and smell.

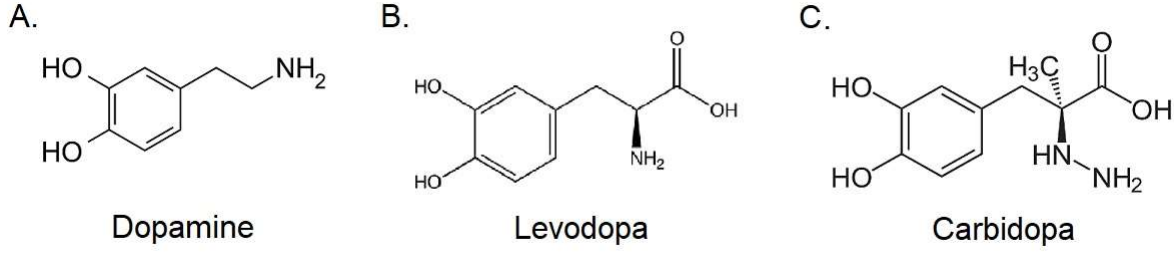

Figure 1: A) DA: neurotransmitter associated with motor function, reward and addiction. B) Levodopa: molecular precursor of DA capable of penetrating the blood-brain barrier, increasing DA production in the brain and manage symptoms. C) Carbidopa: this molecule slows degradation of levodopa by decreasing its peripheral conversion to DA, reducing gastrointestinal side effects and increasing levodopa's bioavailability in the central nervous system [8,9] (Source: Public Domain [10–12]).

the search of new techniques. One of the currently available interventions is the surgically implanted deep brain stimulation [15-19]. Another is the prescription of medical cannabis, which is gaining more adherence of physicians, as regulation reaches several countries and beneficial effects are consistently demonstrated in trials. In more recent developments, stem cell research brings hope to physicians and patients, with its focus on neuroprotection and neurorestorative therapies [20-29], therapeutic benefits not observed in any of the previously available methods.

Epidemiology of PD

PD is a common neurological disorder in older adults, with a prevalence of approximately 1% of individuals over 60 years of age, 2% of those over 65, and 4% of the population older than 85 in the United States [30]. Its average annual incidence is 14 per 100,000 inhabitants of the total population, and 160 per 100,000 inhabitants over 65 years of age in high-income countries. The number of affected patients is predicted to double worldwide by 2030 [3,31].

The risk of developing the pathology is estimated at 2% for men and 1.3% for women aged 40 years and older [30,31]. Data on incidence according to race and ethnicity are few and inconsistent, but it appears to affect all ethnic groups and socioeconomic classes. Prevalence is low before the age of 50, but increases sharply with senescence [32].

The risk of dementia in patients of PD varies among research, with incidences ranging from 30 to 80%, a sharp contrast to the incidence of this condition in the overall population, in which it goes from 5 to 8%. Dementia is a major cause of permanent disability, for currently there are no restorative treatments. Depression is also an important factor to be taken into account, with 47% of PD patients also showing evidence of this pathology [30,33,34].

PD can be hard to diagnose since there is no laboratorial test able to identify it. This lack of molecular or histological diagnosis, therefore, renders it mistakable for other health conditions. Healthcare providers must then stick to medical and family histories, physical examinations, and body imaging. Magnetic resonance imaging and computed tomography scan, for instance, can identify other problems and discard other diseases [31,32].

Basis of the Disease

The etiopathogenesis PD is complex, with environmental and genetic both playing important roles in its development [35-40]. Its motor manifestations are due to discontinuity of the nigrostriatal dopaminergic circuitry (Figure 2A). Another pathological hallmark of PD are the Lewy bodies. These round eosinophilic intracytoplasmic proteinaceous inclusion bodies, structures composed of fibrillar alpha-synuclein (Figure 2B), are present in surviving neurons [39,41]. It is not yet clear if the protein alpha-synuclein is a cause or a compensatory protection.

Some light begins to be shed over this pathogenesis puzzle. Parkinsonism observed in users of contaminated heroin [44] led to the verification of mitochondria abnormalities. Post-mortem tissue of PD patients, as well as animal models of the disease (fly, zebrafish and mouse) also presented decrease in mitochondrial activity and energy production [45-47], and mitochondrial diseases are more prone to damage tissues with bigger energy demands, such as nervous and cardiac tissues [48,49]. The oxidative stress, resultant of this mitochondrial breakdown, harms the neuron's integrity and signals pathways that lead to cell death [35,50-52], and demonstrate the importance of defective mitochondrial activity in PD pathogenesis [27,37,39,51,53,54].

Genetics also plays an important role in PD [4,37,39,55,56]. Two sets of genes are associated with mitochondrial function: mitochondrial DNA (mtDNA) and chromosomal DNA, the latter responsible for mtDNA regulation. The circular mtDNA has 37 genes [57], responsible for encoding 13 proteins essential for the energy machinery (electron transport chain) to work [58]. Mutations can cause changes in the organelle function [38,59], and these accumulate over life, which explains their growing relevance as the patients age.

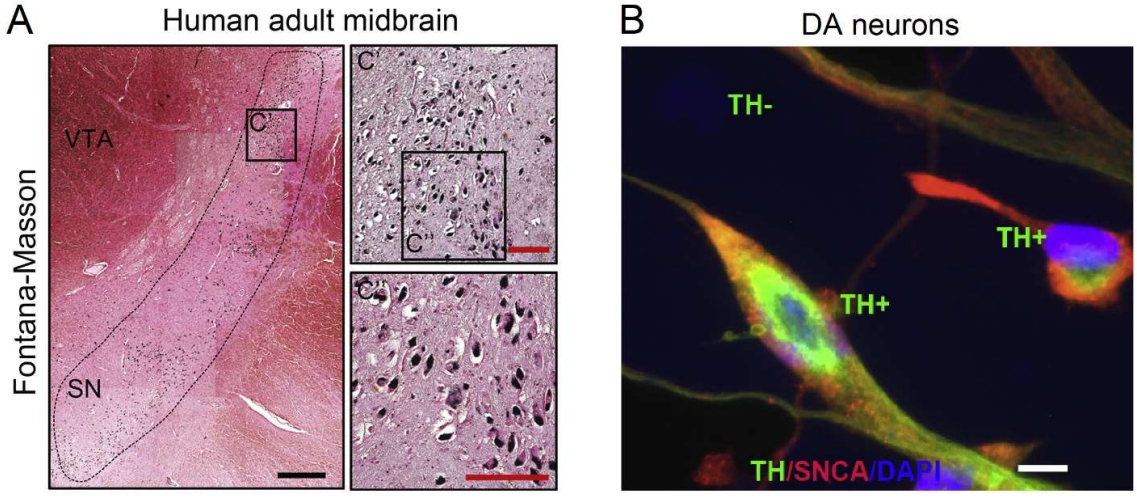

Figure 2: A) High magnification of human adult midbrain post-mortem tissue, with highlight to the *substantia nigra* and to the dark pigment neuromelanin. Black scale bar: 1mm. Red scale bar: 200 µm [28]. B) Alpha-synuclein immunostaining (red) of stem cell derived dopaminergic neurons (green) generated from arm adipose tissue. Nuclei (blue). White scale bar: 10 µm [42]. Motor symptoms appear when 60% to 80% of dopaminergic neurons of the substantia nigra die [43]. (Source: Public Domain).

The best-known gene group associated with PD are PARK genes, because of their importance in the regulation of mitochondrial activity, protein activity, alpha-synuclein production and, consequently, vesicle traffic and neurotransmitter release. This field receives ever more attention. The mechanisms underlying these organelles dysfunction, particularly in familial PD, require further research, making PARK genes a potential target for the development of PD biomarkers for help with diagnosis, and even a target for new treatment alternatives [28,37,49,51,60].

Treatments

Intense physical exercise

High-intensity exercise might modify disease progression [61]. It improves clinical symptoms: pain, mobility, standing balance, posture, has a positive effect in the associated depression and decreases the risk of falls [62-64]. It produces benefits across many body systems, presents few risks, is inexpensive, and showed good adherence with minimal supervision. In rodent PD models, exercise has been shown to not only decrease symptoms but also to reduce underlying disease processes [65]. A high-intensity multimode exercise program tested in PD patients produced more improvement than low-intensity exercise, which also suggests a link between these results and an improved anti-inflammatory profile [66].

These perceived benefits could be consequence of the synthesis and expression of monoaminergic neurotransmitters. DA, together with the brain-derived neurotrophic factor (a growth factor that promotes proliferation and maturation of new neurons), activates the striatum and positively influence motor disorders and neuronal plasticity [63,64,67,68]. This factor is also related to increased dendritic arborization in cortical areas and mitochondrial biogenesis [69], and its role in the regulation of the serotoninergic system [70,71] shows how important adequate amounts of physical exercise are, playing parts both in increasing resilience against PD and helping maintain physical and mental health [63].

Dopaminergic drugs

PD treatment is anchored on pharmacological substitution of striatal DA and non-dopaminergic approaches, addressing both motor and non-motor symptoms. Levodopa, a medication classified as a central nervous system agent, works by being converted to DA, reducing its cerebral deficit. It manages motor symptoms but its conversion in the digestive tract might cause nausea or vomiting. Because of that, it is usually associated with carbidopa (Figure 1C), a decarboxylase inhibitor. This prevents the levodopa degradation that occurs before it reaches the brain, lowering its effective dose and lessening side effects [8,9].

Patients benefit from dopaminergic therapy in the early period after diagnosis. However, as the disease progresses, motor complications and therapeutic fluctuations appear, consequence of an uneven response to levodopa. This hindrance in efficacy is partly due to the loss of the endogenous DA-synthesizing enzyme, L-amino acid decarboxylase. Consequently, patients require higher doses of levodopa and additional therapies to maintain motor function, even though clinical research suggests it does not worsen disease progression [72,73].

One additional therapy is the use of inhibitors of catechol-O-methyltransferase, commonly used as an adjunct to levodopa for the amelioration of wearing-off symptoms. These inhibitors reduce the breakdown of levodopa and increase its plasma half-life, although they may increase dyskinesia [74-76].

Monoamine oxidase B inhibitors block DA degradation and are used to increase its synaptic concentration. There is evidence that monoamine oxidase B inhibitors do exert some neuroprotective properties in the PD models. They are recommended as monotherapy in the early stages of the disease, and as complementary therapy to levodopa in advanced PD [77-79].

DA agonists are another option. They directly stimulate DA receptors, bypassing degenerating dopaminergic neurons in the brain. They help to decrease the frequency of levodopa intake (they possess longer half-life, of 6 hours), but their use has more psychiatric side effects, like somnolence, hallucination, and impulse control disorders [77,80]. DA agonists can be ergoline (first generation) or non-ergoline. The latter are considered a better option, since they bond only to specific receptors, and preserve other pathways for additional pharmacodynamic interventions [3].

Deep brain stimulation

In some cases, symptoms of PD persist despite pharmacologic optimal treatment and, in others, too heavy are the side effects of the medication [3]. In both cases, innovative surgical therapies may be used. One of these therapies is deep brain stimulation. It consists of a pacemaker like device that uses electrical stimulation to alleviate symptoms, reducing tremor significantly. A new generation of brain implants might become available as research groups around the world develop more efficient technology [19,81,82].

Deep brain stimulation implants are surgically inserted. The targeted areas are thalamus and basal ganglia [15]. Placement of electrodes (Figure 3) is done with help of imaging technology, and by real time checking of the stimulation's effect, both precise methods. The United States Food and Drug Administration has already approved indications of deep brain stimulation for essential tremor, PD, obsessive compulsive disorder, and trials are on their way to evaluate its contributions in other disorders, such as depression [83-85]. So great is its success, that it is becoming a viable choice for younger patients, and results have been positive. The implants diminish the need of the medication, softening its side effects [16,86,87].

Medical cannabis

PD non-motor symptoms are not responsive to DA replacement therapy. Among them are pain, anxiety, appetite loss and depression [89]. They usually appear even before the first motor symptoms, and have a dramatic impact on the patients' quality of life.

Opioids are often used to treat neuropathic pain, but over-prescription and addiction associated to this treatment is a worldwide crisis, affecting public health and quality of life [90,91].

Medical cannabis is already one of the strategies used to fight opioid addiction, as well as treating chronic pain, with particular success in neuropathic, surgical and cancer related pains, and shows reduction in opioid consumption [92-94]. Cannabis induced a significant reduction on reported pain intensity, improved assessments of quality of life, was not associated with serious adverse events and was characterized by improvement in treatment perception and low discontinuation rate [95].

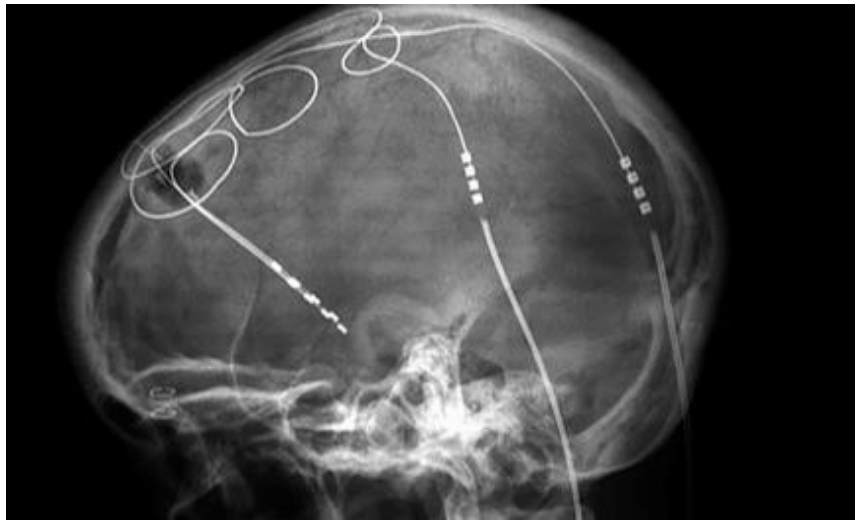

Figure 3: Electrode positioning in deep brain stimulation [88]. (Source: Public Domain)

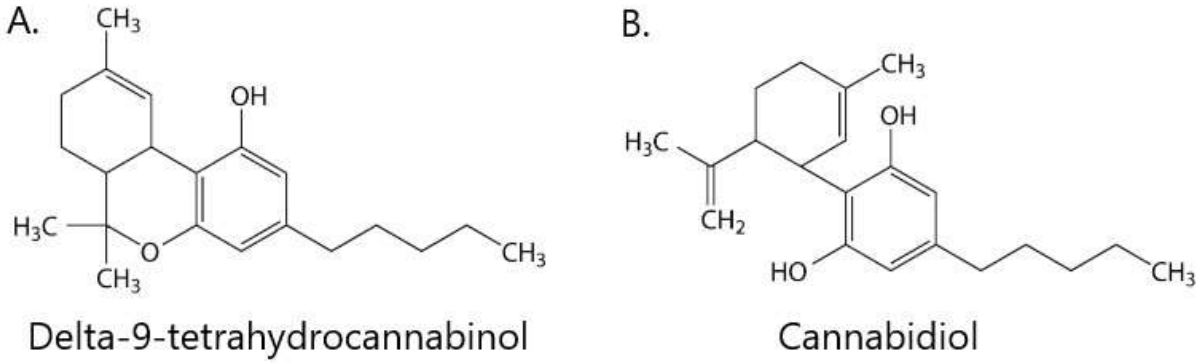

Figure 4: A) The THC molecule is responsible for the psychoactive effects and changes in pain perception, and requires heat to be activated. B) The CBD molecule, devoid of psychoactive euphoriant effects, has anti-inflammatory properties and relieves pain and anxiety [92,93,96-98]. For pain relief, an optimal rate of THC and CBD should be considered for each person, as well as a suitable form of consumption. Edibles containing THC have been associated to anxiety increase [99,100], already a common symptom in PD patients, so these might not be adequate for them. Herb-vaporizers seem to be a better alternative than joints for THC consumption, since they have controlled temperature and produce less residues [101,102] (Source: Public Domain [103]).

Cannabis mostly know components are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) (Figure 4). An advantage to its prescription is its historical use by humanity and demonstrated safety: death by cannabis overdose has never been recorded. Heavy and chronical users, particularly those who begin its use in adolescence, have shown cognition and memory impairment, and long-term effects on DA signaling. Nevertheless, its most common side effects are dizziness, dry mouth and somnolence, and even these are reported by less than 10% of patients. Although dizziness should increase the risk of falls, these have been less frequent during treatment with cannabis [95].

Cannabis compounds have been broadly studied since the 90's. This led to the discovery of the endocannabinoid system and its composition: endocannabinoids (endogenous lipid-based retrograde neurotransmitters) and cannabinoid receptors (proteins present in the vertebrate nervous system). Its involvement in PD is being studied, but it is known that it functions as a neuromodulator, with important roles in the central nervous system, such as regulating development and synaptic plasticity, and orchestrating response to insults [104-109].

Treating pain and diminishing opioid consumption are but a few of the many applications of medical cannabis for PD. Changes of the endocannabinoid signaling have been implicated in other neurological diseases, such as Alzheimer's and multiple sclerosis [110,111]. Medicinal cannabis and its derivatives seem to also function as neuroprotectants, decreasing spasticity in multiple sclerosis [112], and reducing seizures in Lennox–Gastaut syndrome. Adverse events were reported by 86% of patients, mostly mild. It

has also been found to improve patients' scores in the Unified PD Rating Scale, particularly when assessing rigidity, bradykinesia and tremors [113,114].

It is therefore no surprise that the data regarding cannabis usage is increasing, along with regulation or judicial authorization in several countries: Canada, United States, Brazil and Uruguay, among others [115-117]. Epidemiological information show that the older population constitutes a growing segment of medical cannabis users, ranging from approximately 7% to more than a third, depending on the country [95,118]. Since the aging population constitutes a large parcel of neurological patients (with its worldwide number expected to double by 2025), cannabis use is predicted to increase among this demographic. [30].

Hyporexia and depression, both struggles for PD patients, might also be mitigated by cannabis therapeutics. These properties could be beneficial to many other pathologies, such as chemotherapy induced nausea and vomiting, Alzheimer's disease, anorexia nervosa, dementia, dystonia, Huntington's disease, post-traumatic stress disorder, psychosis, Tourette syndrome, epilepsy, and more [106,107,119,120].

Nevertheless, large randomized trials are still needed to confirm the utility of cannabis in chronic pain management and elucidate long-term adverse effects, in both young and elderly populations. Studies must also determine dosage and the best way of administrating these compounds, regarding the clinical aspects of each patient [96,121].

Conclusion

PD is a complex neurodegenerative disease with a heterogeneous aspect, requiring a multidisciplinary approach in order to be appropriately addressed [3,4,35]. Exciting research is being done on its etiology and pathogenesis, and wearable technologies [122,123] bring information for physicians and researchers in real time. As current treatments evolve and their precision improves, they help patients cope with motor and no motor symptoms, while reducing side effects. For now, treatments are symptomatic only, but animal models and *in vitro* investigation might accelerate drug discovery and help elucidate genetic and neuroprotectant mechanisms [124]. As more of the brain development and aging is understood, it becomes apparent that events thought to happen only in brain development remain in some parts of the developed brain, like neurotransmitter switching. Unveiling the role of neurotransmitter switching in PD pathogenesis could lead to a new front of research [125,126]. At the same time, stem cells slowly gain recognition as a viable therapy, not only in restoring lost cells, but also in modulating chronic neuroinflammation [127-135]. The results in these fronts could lead to the discovery of early biomarkers and even a stop or a reversion to PD.

Declarations

Authors have contributed to the manuscript elaboration, editing and reviewing, and declare no conflict of interest.

References

1. Anticoli S, Bravi MC, Mazza S, Pezzella FR, Pandis MF. Vascular Parkinsonism: Motor and Non-Motor Response on Treatment with Rotigotine. J Bioanal Biomed. 2017;09(02):1–3
2. Fortaleza FR. Vascular Parkinsonism and Cognitive Impairment without Lobar Hemorrhage related to Cerebral Amyloid Angiopathy. Ann Behav Neurosci 2019;2(1):144–8.
3. Zesiewicz TA. Parkinson disease. CONTINUUM: Lifelong Learning in Neurology. 2019 Aug 1;25(4):896-918.
4. Balestrino R, Schapira AH. Parkinson disease. European Journal of Neurology. 2020 Jan;27(1):27-42
5. Obeso JA, Stamelou M, Goetz CG, Poewe W, Lang AE, Weintraub D, et al. Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy. Movement Disorders. 2017 Sep;32(9):1264-310.
6. Carlsson A, Lindqvist M, Magnusson TO. 3,4-Dihydroxyphenylalanine and 5-Hydroxytryptophan as reserpine antagonists. Nature. 1957 Nov;180(4596):1200.
7. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. New England Journal of Medicine. 1967 Feb 16;276(7):374-9.
8. Labeit B, Claus I, Muhle P, Suntrup-Krueger S, Dziewas R, Warnecke T. Effect of intestinal levodopa-carbidopa infusion on pharyngeal dysphagia: results from a retrospective pilot study in patients with Parkinson's disease. Parkinson's Disease. 2020 Mar 11;2020.
9. Hinz M, Stein A, Cole T. Parkinson's disease: carbidopa, nausea, and dyskinesia. Clinical Pharmacology: Advances and Applications. 2014;6:189.
10. Harbin. Carbidopa2. Wikimedia Commons. 2009. Available from: https://commons.wikimedia.org/w/index.php?curid=1219045
11. Harbin. Dopamine. Wikimedia Commons. 2008. Available from: https://commons.wikimedia.org/w/index.php?curid=1666908
12. Techelf. Levodopa. Wikimedia Commons. 2006. Available from: https://commons.wikimedia.org/w/index.php?curid=1913318
13. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment Guidelines. Neurology. 2001 Jun 12;56(suppl 5):S1-88.
14. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Movement disorders: official journal of the Movement Disorder Society. 2001 May;16(3):448-58.
15. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. The Lancet Neurology. 2009 Jan 1;8(1):67-81.
16. University of Michigan Health, Michigan Medicine. Deep Brain Stimulation; 2018 [cited 2020 Apr 11]. Available at: https://www.uofmhealth.org/conditions-treatments/brain-neurological-conditions/deep-brain-stimulation
17. Mitchell KT, Larson P, Starr PA, Okun MS, Wharen Jr RE, Uitti RJ et al. Benefits and risks of unilateral and bilateral ventral intermediate nucleus deep brain stimulation for axial essential tremor symptoms. Parkinsonism & Related Disorders. 2019 Mar 1;60:126-32
18. Mirzadeh Z, Chapple K, Lambert M, Evidente VG, Mahant P, Ospina MC, et al. Parkinson's disease outcomes after intraoperative CT-guided "asleep" deep brain stimulation in the globus pallidus internus. Journal of Neurosurgery. 2016 Apr 1;124(4):902-7.
19. de Carvalho BF, Marques LM, Nogueira IC, Barreto GN. Electronic adjuvants to understand and modulate the brain. Journal of Neurobiology. 2019;1(1):5-9.
20. Chemmarappally JM, Pegram HC, Abeywickrama N, Fornari E,

Hargreaves AJ, De Girolamo LA, et al. A Co-Culture nanofibre scaffold model of neural cell degeneration in relevance to Parkinson's disease. Scientific Reports. 2020 Feb 17;10(1):1-4.

21. Korecka JA, Talbot S, Osborn TM, de Leeuw SM, Levy SA, Ferrari EJ, et al. Neurite collapse and altered ER Ca2+ control in human Parkinson disease patient iPSC-derived neurons with LRRK2 G2019S mutation. Stem Cell Reports. 2019 Jan 8;12(1):29-41

22. Wakeman DR, Hiller BM, Marmion DJ, McMahon CW, Corbett GT, Mangan KP, et al. Cryopreservation maintains functionality of human iPSC dopamine neurons and rescues parkinsonian phenotypes in vivo. Stem Cell Reports. 2017 Jul 11;9(1):149-61.

23. Kriks S, Shim JW, Piao J, Ganat YM, Wakeman DR, Xie Z, et al. Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease. Nature. 2011 Dec;480(7378):547-51.

24. Kirkeby A, Grealish S, Wolf DA, Nelander J, Wood J, Lundblad M, et al. Generation of regionally specified neural progenitors and functional neurons from human embryonic stem cells under defined conditions. Cell Reports. 2012 Jun 28;1(6):703-14.

25. Kikuchi T, Morizane A, Doi D, Magotani H, Onoe H, Hayashi T, et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. Nature. 2017 Aug;548(7669):592-6.

26. Monzel AS, Smits LM, Hemmer K, Hachi S, Moreno EL, van Wuellen T, et al. Derivation of human midbrain-specific organoids from neuroepithelial stem cells. Stem Cell Reports. 2017 May 9;8(5):1144-54.

27. Chung SY, Kishinevsky S, Mazzulli JR, Graziotto J, Mrejeru A, Mosharov EV, et al. Parkin and PINK1 patient iPSC-derived midbrain dopamine neurons exhibit mitochondrial dysfunction and α-synuclein accumulation. Stem Cell Reports. 2016 Oct 11;7(4):664-77.

28. Jo J, Xiao Y, Sun AX, Cukuroglu E, Tran HD, Göke J, et al. Midbrain-like organoids from human pluripotent stem cells contain functional dopaminergic and neuromelanin-producing neurons. Cell Stem Cell. 2016 Aug 4;19(2):248-57.

29. Ma L, Hu B, Liu Y, Vermilyea SC, Liu H, Gao L, et al. Human embryonic stem cell-derived GABA neurons correct locomotion deficits in quinolinic acid-lesioned mice. Cell Stem Cell. 2012 Apr 6;10(4):455-64.

30. World Health Organization. Neurological disorders: Public Health. World Health Organization. 2020.

31. De Lau LM, Breteler MM. Epidemiology of Parkinson's disease. The Lancet Neurology. 2006 Jun 1;5(6):525-35.

32. Elbaz A, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Risk tables for parkinsonism and Parkinson's disease. Journal of Clinical Epidemiology. 2002 Jan 1;55(1):25-31.

33. Hanagasi HA, Tufekcioglu Z, Emre M. Dementia in Parkinson's disease. J Neurol Sci. 2017;374(2016):26–31.

34. Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, et al. A population-based investigation of Parkinson's disease with and without dementia: Relationship to age and gender. Archives of Neurology. 1992 May 1;49(5):492-7.

35. Lin MT, Cantuti-Castelvetri I, Zheng K, Jackson KE, Tan YB, Arzberger T, et al. Somatic mitochondrial DNA mutations in early Parkinson and incidental Lewy body disease. Annals of Neurology. 2012 Jun;71(6):850-4.

36. Gowers WR. A Manual of Diseases of the Nervous System: Diseases of the Spinal Cord and Nerves. P. Blakiston, Son & Company. 1886.

37. Larsen SB, Hanss Z, Krüger R. The genetic architecture of mitochondrial dysfunction in Parkinson's disease. Cell and Tissue Research. 2018 Jul;373(1):21-37.

38. Follett J, Bugarcic A, Yang Z, Ariotti N, Norwood SJ, Collins BM, et al. Parkinson disease-linked Vps35 R524W mutation impairs the endosomal association of retromer and induces α-synuclein aggregation. Journal of Biological Chemistry. 2016 Aug 26;291(35):18283-98.

39. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease: Molecular mechanisms and pathophysiological consequences. The EMBO Journal. 2012 Jul 18;31(14):3038-62.

40. Wang A, Costello S, Cockburn M, Zhang X, Bronstein J, Ritz B. Parkinson's disease risk from ambient exposure to pesticides. European Journal of Epidemiology. 2011 Jul 1;26(7):547-55.

41. Walker L, Stefanis L, Attems J. Clinical and neuropathological differences between Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies – current issues and future directions. J Neurochem 2019;150(5):467–74.

42. Yang SY, Beavan M, Chau KY, Taanman JW, Schapira AH. A human neural crest stem cell-derived dopaminergic neuronal model recapitulates biochemical abnormalities in GBA1 mutation carriers. Stem Cell Reports. 2017 Mar 14;8(3):728-42.

43. Hirsch E, Graybiel AM, Agid YA. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature. 1988 Jul;334(6180):345-8.

44. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 1983 Feb 25;219(4587):979-80.

45. Shim JH, Yoon SH, Kim KH, Han JY, Ha JY, Hyun DH, et al. The antioxidant Trolox helps recovery from the familial Parkinson's disease-specific mitochondrial deficits caused by PINK1-and DJ-1-deficiency in dopaminergic neuronal cells. Mitochondrion. 2011 Sep 1;11(5):707-15.

46. Palacino JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, et al. Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. Journal of Biological Chemistry. 2004 Apr 30;279(18):18614-22.

47. Greene JC, Whitworth AJ, Kuo I, Andrews LA, Feany MB, Pallanck LJ. Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants. Proceedings of the National Academy of Sciences. 2003 Apr 1;100(7):4078-83.

48. Chan DC. Mitochondria: Dynamic organelles in disease, aging, and development. Cell. 2006 Jun 30;125(7):1241-52.

49. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson's disease. J Neurochem. 2016;139:216–31.

50. Guglielmi V, Marini M, Tomelleri G, Vattemi G. Over Expression of NOS2 in Ragged-red Fibers from Patients with Mitochondrial Disorders due to Mutations in mtDNA. Ann Behav Neurosci. 2018;1(1):07–13.

51. Moon HE, Paek SH. Mitochondrial dysfunction in Parkinson's disease. Experimental Neurobiology. 2015 Jun;24(2):103.

52. Deas E, Cremades N, Angelova PR, Ludtmann MH, Yao Z, Chen S, et al. Alpha-synuclein oligomers interact with metal ions to induce oxidative stress and neuronal death in Parkinson's disease. Antioxidants & Redox Signaling. 2016 Mar 1;24(7):376-91.

53. Dagda RK, Pien I, Wang R, Zhu J, Wang KZ, Callio J, et al. Beyond the mitochondrion: cytosolic PINK 1 remodels dendrites through

Protein Kinase A. Journal of Neurochemistry. 2014 Mar;128(6):864-77.

54. Deng H, Dodson MW, Huang H, Guo M. The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in Drosophila. Proceedings of the National Academy of Sciences. 2008 Sep 23;105(38):14503-8.

55. Poole AC, Thomas RE, Andrews LA, McBride HM, Whitworth AJ, Pallanck LJ. The PINK1/Parkin pathway regulates mitochondrial morphology. Proceedings of the National Academy of Sciences. 2008 Feb 5;105(5):1638-43.

56. Roosen DA, Blauwendraat C, Cookson MR, Lewis PA. DNAJC proteins and pathways to parkinsonism. The FEBS Journal. 2019 Aug;286(16):3080-94.

57. Wittenhagen LM, Kelley SO. Dimerization of a pathogenic human mitochondrial tRNA. Nature Structural Biology. 2002 Aug;9(8):586-90.

58. Tu YT, Barrientos A. The human mitochondrial DEAD-box protein DDX28 resides in RNA granules and functions in mitoribosome assembly. Cell Reports. 2015 Feb 17;10(6):854-64.

59. Wang W, Wang X, Fujioka H, Hoppel C, Whone AL, Caldwell MA, et al. Parkinson's disease–associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. Nature Medicine. 2016 Jan;22(1):54-63.

60. 60. Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harbor Perspectives in Medicine. 2012 Jan 1;2(1):a008888.

61. Combs-Miller SA, Moore ES. Predictors of outcomes in exercisers with Parkinson disease: a two-year longitudinal cohort study. NeuroRehabilitation. 2019 Jan 1;44(3):425-32.

62. Tollár J, Nagy F, Kovács N, Hortobágyi T. A high-intensity multicomponent agility intervention improves Parkinson patients' clinical and motor symptoms. Archives of Physical Medicine and Rehabilitation. 2018 Dec 1; 99(12):2478-84.

63. Oliveira de Carvalho A, Murillo-Rodriguez E, Rocha NB, Carta MG, Machado S. Physical exercise for parkinson's disease: clinical and experimental evidence. Clinical Practice & Epidemiology in Mental Health. 2018 Mar 30;14(1).

64. Marais L, Stein DJ, Daniels WM. Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats. Metabolic Brain Disease. 2009 Dec;24(4):587-97.

65. Dutra MF, Jaeger M, Ilha J, Kalil-Gaspar PI, Marcuzzo S, Achaval M. Exercise improves motor deficits and alters striatal GFAP expression in a 6-OHDA-induced rat model of Parkinson's disease. Neurological Sciences. 2012 Oct;33(5):1137-44.

66. Landers MR, Navalta JW, Murtishaw AS, Kinney JW, Richardson SP. A high-intensity exercise boot camp for persons with Parkinson disease: a phase II, pragmatic, randomized clinical trial of feasibility, safety, signal of efficacy, and disease mechanisms. Journal of Neurologic Physical Therapy. 2019 Jan 1;43(1):12-25.

67. Kawashima S, Ueki Y, Kato T, Matsukawa N, Mima T, Hallett M, et al. Changes in striatal dopamine release associated with human motor-skill acquisition. PloS One. 2012 Feb 15;7(2):e31728.

68. Huang F, Wu Y, Wang H, Chang J, Ma G, Yin Z. Effect of controlled release of brain-derived neurotrophic factor and neurotrophin-3 from collagen gel on neural stem cells. NeuroReport. 2016 Jan 20;27(2):116-23.

69. Puigserver P, Spiegelman BM. Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α): transcriptional coactivator and metabolic regulator. Endocrine Reviews. 2003 Feb 1;24(1):78-90.

70. Kronenberg G, Mosienko V, Gertz K, Alenina N, Hellweg R, Klempin F. Increased brain-derived neurotrophic factor (BDNF) protein concentrations in mice lacking brain serotonin. European Archives of Psychiatry and Clinical Neuroscience. 2016 Apr 1;266(3):281-4.

71. Mössner R, Daniel S, Albert D, Heils A, Okladnova O, Schmitt A, et al. Serotonin transporter function is modulated by brain-derived neurotrophic factor (BDNF) but not nerve growth factor (NGF). Neurochemistry International. 2000 Mar 1;36(3):197-202.

72. Nutt JG, Curtze C, Hiller A, Anderson S, Larson PS, Van Laar AD, et al. Aromatic L-amino acid decarboxylase gene therapy enhances levodopa response in Parkinson's disease. Movement Disorders. 2020 May; 35(5):851-8.

73. Ciesielska A, Samaranch L, San Sebastian W, Dickson DW, Goldman S, Forsayeth J, et al. Depletion of AADC activity in caudate nucleus and putamen of Parkinson's disease patients; implications for ongoing AAV2-AADC gene therapy trial. PLoS One. 2017 Feb 6;12(2):e0169965.

74. Müller T. Catechol-O-methyltransferase inhibitors in Parkinson's disease. Drugs. 2015 Feb;75(2):157-74.

75. Solís O, García-Montes JR, Garcia-Sanz P, Herranz AS, Asensio MJ, Kang G, et al. Human COMT over-expression confers a heightened susceptibility to dyskinesia in mice. Neurobiology of Disease. 2017 Jun 1;102:133-9.

76. Marin C, Obeso JA. Catechol-O-methyltransferase inhibitors in preclinical models as adjuncts of L-dopa treatment. International Review of Neurobiology. 2010 Jan 1;95:191-205.

77. PD Med Collaborative Group, Gray R, Ives N, Rick C, Patel S, Gray A, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. The Lancet. 2014 Sep 27;384(9949):1196-205.

78. Dezsi L, Vecsei L. Monoamine oxidase B inhibitors in Parkinson's disease. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2017 May 1;16(4):425-39.

79. Schapira AH. Monoamine oxidase B inhibitors for the treatment of Parkinson's disease. CNS Drugs. 2011 Dec;25(12):1061-71.

80. Voon V, Gao J, Brezing C, Symmonds M, Ekanayake V, Fernandez H, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's; disease. Brain. 2011 May 1;134(5):1438-46.

81. Pisarchik AN, Maksimenko VA, Hramov AE. From novel technology to novel applications: Comment on "An integrated brain-machine interface platform with thousands of channels" by Elon Musk and Neuralink. Journal of Medical Internet Research. 2019;21(10):e16356.

82. Juavinett AL, Bekheet G, Churchland AK. Chronically implanted Neuropixels probes enable high-yield recordings in freely moving mice. elife. 2019 Aug 14;8:e47188.

83. van der Wal JM, Bergfeld IO, Lok A, Mantione M, Figee M, Notten P, et al. Long-term deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression. Journal of Neurology, Neurosurgery & Psychiatry. 2020 Feb 1;91(2):189-95.

84. Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. The Lancet Psychiatry. 2017 Nov 1;4(11):839-49.

85. Gouveia FV, Hamani C. Deep brain stimulation as a treatment for depressive disorder. Brazilian Journal of Psychiatry. 2020 Mar 9;42:342-3.

86. Northwestern Medicine. Deep brain stimulation surgery. Northwestern Medicine. 2012 [cited 2020 Apr 11].

87. Bucholz R. The Deep Brain Stimulation (DBS) Journey. SSM Health Saint Louis University Hospital. 2011 [cited 2020 Apr 11]. Available from: https://www.youtube.com/watch?v=ksjHNbb6NFQ

88. Hacking C, Gaillard F. Deep Brain Stimulation.jpg. Wikimedia Commons. 2013. [cited 2020 Apr 11]. Available from: https://commons.wikimedia.org/wiki/File:Deep_Brain_Stimulation.jpg

89. Maillet A, Krack P, Lhommée E, Météreau E, Klinger H, Favre E, et al. The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. Brain. 2016 Sep 1;139(9):2486-502.

90. Volkow ND, Collins FS. The role of science in addressing the opioid crisis. New England Journal of Medicine. 2017 Jul 27;377(4):391-4.

91. Powell D, Pacula RL, Taylor E. How increasing medical access to opioids contributes to the opioid epidemic: evidence from Medicare Part D. Journal of Health Economics. 2020 May 1;71:102286.

92. Park JY, Wu LT. Prevalence, reasons, perceived effects, and correlates of medical marijuana use: a review. Drug and Alcohol Dependence. 2017 Aug 1;177:1-3.

93. Fairman BJ. Trends in registered medical marijuana participation across 13 US states and District of Columbia. Drug and Alcohol Dependence. 2016 Feb 1;159:72-9.

94. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. International Journal of Drug Policy. 2017 Apr 1;42:30-5.

95. Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. European Journal of Internal Medicine. 2018 Mar 1;49:44-50.

96. Ryan-Ibarra S, Induni M, Ewing D. Prevalence of medical marijuana use in C alifornia, 2012. Drug and Alcohol Review. 2015 Mar;34(2):141-6.

97. Machado Bergamaschi M, Helena Costa Queiroz R, Waldo Zuardi A, Crippa AS. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Current Drug Safety. 2011 Sep 1;6(4):237-49.

98. Formukong EA, Evans AT, Evans FJ. Analgesic and antiinflammatory activity of constituents of Cannabis sativa L. Inflammation. 1988 Aug;12(4):361-71.

99. Barrus DG, Capogrossi KL, Cates SC, Gourdet CK, Peiper NC, Novak SP, et al. Tasty THC: promises and challenges of cannabis edibles. Methods Report (RTI Press). 2016 Nov;2016.

100. Lamy FR, Daniulaityte R, Sheth A, Nahhas RW, Martins SS, Boyer EW, Carlson RG. "Those edibles hit hard": Exploration of Twitter data on cannabis edibles in the US. Drug and Alcohol Dependence. 2016 Jul 1;164:64-70.

101. Gartner CE. Mull it over: cannabis vaporizers and harm reduction. Addiction. 2015 Oct 16;110(11):1709-10.

102. Hansson A, Rankin G, Uski O, Sehlstedt M, Bosson J, Pourazar J, et al. Wood smoke effects on epithelial cell lines and human airway cells. Eur Respir J. 2019;54(Suppl. 63):PA5448.

103. Seekpng. Structural Formulas Thc -cbd - Thc Vs Cbd Formula. Seekpng. [cited 2020 Apr 11]. Available from: https://www.seekpng.com/ipng/u2e6t4o0e6u2r5y3_structural-formulas-thc-cbd-thc-vs-cbd-formula/

104. Battista N, Di Tommaso M, Bari M, Maccarrone M. The endocannabinoid system: an overview. Frontiers in Behavioral Neuroscience. 2012 Mar 14;6:9.

105. Mechoulam R, Parker LA. The endocannabinoid system and the brain. Annual Review of Psychology. 2013 Jan 3;64:21-47.

106. Woodhams SG, Sagar DR, Burston JJ, Chapman V. The role of the endocannabinoid system in pain. Pain Control. 2015:119-43.

107. Huang WJ, Chen WW, Zhang X. Endocannabinoid system: Role in depression, reward and pain control. Molecular Medicine Reports. 2016 Oct 1;14(4):2899-903.

108. Pisani V, Madeo G, Tassone A, Sciamanna G, Maccarrone M, Stanzione P, et al. Homeostatic changes of the endocannabinoid system in Parkinson's disease. Movement Disorders. 2011 Feb 1;26(2):216-22.

109. Concannon RM, Okine BN, Finn DP, Dowd E. Differential upregulation of the cannabinoid CB2 receptor in neurotoxic and inflammation-driven rat models of Parkinson's disease. Experimental Neurology. 2015 Jul 1;269:133-41.

110. Basavarajappa BS, Shivakumar M, Joshi V, Subbanna S. Endocannabinoid system in neurodegenerative disorders. Journal of Neurochemistry. 2017 Sep;142(5):624-48.

111. Schmöle AC, Lundt R, Toporowski G, Hansen JN, Beins E, Halle A, et al. Cannabinoid receptor 2-deficiency ameliorates disease symptoms in a mouse model with Alzheimer's disease-like pathology. Journal of Alzheimer's Disease. 2018 Jan 1;64(2):379-92.

112. Wade DT, Collin C, Stott C, Duncombe P. Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. Multiple Sclerosis Journal. 2010 Jun;16(6):707-14.

113. Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (medical marijuana) treatment for motor and non–motor symptoms of Parkinson disease: An open-label observational study. Clinical Neuropharmacology. 2014 Mar 1;37(2):41-4.

114. Kolb B, Saber H, Fadel H, Rajah G. The endocannabinoid system and stroke: A focused review. Brain Circulation. 2019 Jan;5(1):1.

115. Abrace Esperança HOME [Internet]. [cited 2020 Apr 11]. Available from: https://abraceesperanca.org.br/home/

116. Hamilton HA, Brands B, Ialomiteanu AR, Mann RE. Therapeutic use of cannabis: Prevalence and characteristics among adults in Ontario, Canada. Canadian Journal of Public Health. 2017 May;108(3):e282-7.

117. Palermo PG. The Uruguayan model of regulating cannabis–legal and geopolitical questions. Zeitschrift für die gesamte Strafrechtswissenschaft. 2018 Oct 25;130(3):859-908.

118. Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. Journal of Psychoactive Drugs. 2013 Jul 1;45(3):199-210.

119. Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clinical Psychopharmacology and Neuroscience. 2017 Nov;15(4):301-312.

120. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015 Jun 23;313(24):2456-73.

121. Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. Journal of Psychoactive Drugs. 2011 Apr 1;43(2):128-35.

122. Patel S, Lorincz K, Hughes R, Huggins N, Growdon J, Standaert D, et al. Monitoring motor fluctuations in patients with Parkinson's disease using wearable sensors. IEEE Transactions on Information Technology in Biomedicine. 2009 Oct 20;13(6):864-73.

123. Maetzler W, Domingos J, Srulijes K, Ferreira JJ, Bloem BR. Quantitative wearable sensors for objective assessment of Parkinson's disease. Movement Disorders. 2013 Oct;28(12):1628-37.

124. Tandé D, Höglinger G, Debeir T, Freundlieb N, Hirsch EC, François C. New striatal dopamine neurons in MPTP-treated macaques result from a phenotypic shift and not neurogenesis. Brain. 2006 May 1;129(5):1194-200.

125. Spitzer NC. Neurotransmitter switching? No surprise. Neuron. 2015 Jun 3;86(5):1131-44.

126. Spitzer NC. Neurotransmitter switching in the developing and adult brain. Annual Review of Neuroscience. 2017 Jul 25;40:1-9.

127. Peruzzotti-Jametti L, Bernstock JD, Vicario N, Costa AS, Kwok CK, Leonardi T, et al. Macrophage-derived extracellular succinate licenses neural stem cells to suppress chronic neuroinflammation. Cell Stem Cell. 2018 Mar 1;22(3):355-68.

128. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Translational Neurodegeneration. 2015 Dec;4(1):1-9.

129. Chao YX, He BP, Tay SS. Mesenchymal stem cell transplantation attenuates blood brain barrier damage and neuroinflammation and protects dopaminergic neurons against MPTP toxicity in the substantia nigra in a model of Parkinson's disease. Journal of Neuroimmunology. 2009 Nov 30;216(1-2):39-50.

130. Gao HM, Zhang F, Zhou H, Kam W, Wilson B, Hong JS. Neuroinflammation and α-synuclein dysfunction potentiate each other, driving chronic progression of neurodegeneration in a mouse model of Parkinson's disease. Environmental Health Perspectives. 2011 Jun;119(6):807-14.

131. Zhang Q, Wu HH, Wang Y, Gu GJ, Zhang W, Xia R. Neural stem cell transplantation decreases neuroinflammation in a transgenic mouse model of Alzheimer's disease. Journal of Neurochemistry. 2016 Feb;136(4):815-25.

132. Kokaia Z, Lindvall O. Sensors of succinate: neural stem cell grafts fight neuroinflammation. Cell Stem Cell. 2018 Mar 1;22(3):283-5.

133. de Carvalho BF, Barreto GN, Marques LM, Machado MMP, Pinto LSS. Stem Cells Treatment to Parkinson's Disease : Perspectives. Ann Behav Neurosci. 2020;3(1):291–7

134. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. Journal of Neurochemistry. 2016 Oct;139:318-24.

135. Pfeiffer RF. Non-motor symptoms in Parkinson's disease. Parkinsonism & Related Disorders. 2016 Jan 1;22:S119-22.