Malta Medical Journal, 32 (1): Pages (2020)
http://mmsjournals.org/index.php/mmj/article/view/144

MMJ

REVIEW ARTICLE

Parkinson's Disease - Current Treatments and the Possible Use of Cannabis

Joseph Ignatius Azzopardi, Peter Ferry

Parkinson's disease is a progressive neurodegenerative movement disorder common in old age. The current prevalence of this condition in the western world is estimated to be 0.3% of the entire population, and this value is expected to increase due to the ageing world population.

Although there is no cure for Parkinson's disease, many therapies aimed to relieve patients from its motor and/or non-motor symptoms exist, both pharmacological and surgical such as levodopa and deep brain stimulation, respectively. However, these therapies have their own problems and disadvantages, for instance levodopa-induced dyskinesia.

As there is currently a movement bringing about the legalisation of cannabis use for medicinal purposes, many studies are being carried out to discover if cannabis or cannabinoids can be used as a treatment modality, hopefully with less side effects than current treatments, to alleviate patients suffering from Parkinson's disease from their symptoms.

In this paper we seek to review the current treatment options available to these patients and what the latest studies in cannabinoids have determined with regards to their use in Parkinson's disease.

Joseph Ignatius Azzopardi*
BSc (Hons)
Faculty of Medicine and Surgery,
University of Malta,
Msida, Malta
joseph.azzopardi.09@um.edu.mt

Peter Ferry
M.D., M.Sc.(Keele), M.R.C.P.(UK),
Dip.Ger.,Dip.O.R.T.(Dundee),
Cert.Med.E.D.(Dundee)
Department of Geriatrics,
Karen Grech Hospital,
Pieta, Malta

*Corresponding author

Parkinson's Disease ... What's in a Name?

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder – it is the commonest movement disorder and the second commonest neurodegenerative disorder following Alzheimer disease, occurring mostly in old age. The current prevalence of PD in the western world is estimated to be 0.3% of the entire population, rising to 1% in people aged over 60, with the prevalence expected to increase as the size of the geriatric population in many countries is on the rise.[1–4]

The disease was described for the first time in 1817 by Dr James Parkinson calling it a "shaking palsy".[5] While the disease is mostly characterised by its motor symptoms such as bradykinesia, gait disturbance, rigidity and a resting tremor; non-motor symptoms such as depression, apathy, anxiety, insomnia, orthostatic hypotension, erectile dysfunction, constipation and fatigue amongst others can also occur.[6]

Pathologically, PD is characterised by the loss of the dopaminergic neurons found in the substantia nigra pars compacta and the presence of Lewy bodies and Lewy neurites in the remaining neurons. Onset of symptoms occurs when approximately 80% of the dopaminergic neurons in the substantia nigra are lost.[7]

A Short History of Medical Cannabis

The medicinal use of cannabis (*Cannabis sativa*) spans thousands of years, with the earliest written evidence being found in the world's first pharmacopeia – *pen-ts'ao ching* – which was based on oral traditions passed from one generation to another since 2,7000 B.C.[8-9]

The introduction of cannabis as a form of medication in Western medicine was made possible by the work of Dr William Brooke O'Shaughnessy, an Irish physician. The use of cannabis for medical purposes then became widely disseminated by the 19th century.[9]

In the 1930's and 1940's however, the medical use of cannabis quickly fell out of use due to fears of the socially deviant behaviours which were attributed to the recreational use of this drug, leading to many countries banning the cannabis from its use in medicine. Things have recently started to change, with many countries, including Cyprus, Malta and the United Kingdom starting to overturn their ban on the use of cannabis in medicine.[9–12]

Despite the recent legalisation of marijuana, a recent survey has showed that many experts in the field of PD still have a lack of knowledge in how cannabis can be used in the treatment of PD, probably because of the lack of high-quality data and education about the effects of cannabis on this disorder.[13] The aim of this review is to bring the latest information about cannabis use in the treatment of Parkinson's disease in one document to facilitate the acquirement of knowledge about this subject.

Current Modalities of Treatment of PD and their Caveats

No cure for PD has yet been found, therefore all current treatments are strictly symptomatic; they can neither halt nor reverse the progressive nature of this disease. The current drugs marketed for the treatment of PD symptoms work either by increasing the dopamine levels in the brain or by mimicking the effects of dopamine.[7]

Levodopa

The gold-standard treatment for PD is levodopa, a dopamine precursor which it breaks down into dopamine once in the brain. To prevent its breakdown in the periphery, levodopa is co-administered with a DOPA-decarboxylase inhibitor such as carbidopa or benserazide. The use of levodopa is not without its problems; for instance, it is ineffective for the control of non-motor symptoms of PD. Furthermore, 'on-off' and 'end-of-dose' motor fluctuations frequently occur after several years of treatment with this drug.[7] Controversy on whether levodopa is actually toxic to dopaminergic neurons also exists.[14]

COMT Inhibitors

Catechol-O-methyl transferase (COMT) inhibitors such as entacapone are commonly used as adjuncts to co-beneldopa and co-careldopa such as in Stalevo to overcome motor fluctuations.[15]

Common side effects of entacapone include constipation, orthostatic hypotension (which could theoretically increase the risk of fractures from falling) and confusion. Caution must be taken when entacapone is prescribed to individuals with a history of ischaemic heart disease as this drug is known to increase its risk.[16-17]

Tolcapone, another COMT inhibitor effective in the control of motor fluctuations has been reported to have caused four cases of acute hepatotoxicity resulting in three fatalities. As a result, the use of this drug has been either completely withdrawn or severely restricted in many countries.[18–21]

Dopamine Receptor Agonists

Dopamine receptor agonists (DRAs) are another modality of treatment of PD, whereby they stimulate dopamine receptors by mimicking the dopamine molecule. DRAs can be used as adjuncts to levodopa in the advanced stages of PD or as monotherapy during the initial stages of PD to delay the need for levodopa.[7,22]

DRAs can be divided into two main classes; the ergot derivatives such as pergolide, and the non-ergot derivatives such as pramipexole and ropinirole. The latter are preferred over the former because of the risks of retroperitoneal fibrosis, pleuropulmonary fibrosis and fibrotic heart valvular disease associated with their use.[23-24]

The non-ergot derivates are not without their problems as they are associated with compulsive gambling and hypersexual behaviour.[25]

MAO-B Inhibitors

Monoamine oxidase B (MAO-B) inhibitors such as rasagiline inhibit the metabolism of dopamine such that they enhance the effect of levodopa if they are used in conjunction.[7]

Patients on MOA-B inhibitors must be advised to limit their intake of tyramine as a potentially lethal hypertensive crisis can result when large amounts of this amino acid are consumed.[26]

Amantadine

Amantadine, an aminoadamantane originally used as an antiviral agent, is a non-competitive NMDA receptor antagonist which is now being used to treat early PD symptoms, and increasingly more as a treatment for dyskinesias caused by levodopa in those with

advanced PD.[27–29] However, several clinical studies have shown that treating PD patients with amantadine prior to initiating levodopa treatment is ineffective in delaying or reducing the onset of levodopa-induced dyskinesias.[30,31]

Some clinical trials have also shown a relation between amantadine treatment and a reduction in the previously mentioned 'impulse control disorders' found in PD patients.[32,33] The author of one of these studies hypothesise that this reduction could be due to the anti-glutamatergic properties of amantadine.[33] While the results from these studies are encouraging, further clinical trials, which are larger in size, are needed to shed more light on the possible use of this drug as a treatment modality for impulse control disorders in PD patients.

Unfortunately, both the use and the withdrawal of amantadine are marred by a range of adverse effects, which might make the clinician cautious about using this drug as the risks might easily outweigh any benefit that treatment with this drug may convey.

Side effects of amantadine treatment on the vision and eyes have been reported widely, including oculogyric crises, visual loss, mydriasis, corneal oedema and hallucinations amongst others.[34–36]

Some papers also report some interesting cases where the use or withdrawal of amantadine in PD was associated with adverse effects not usually attributed to it, such as the development of patulous Eustachian tubes (PET),[37] dropped head syndrome,[38] severe psychosis,[39] right ventricular outflow tract tachycardia[40] and syndrome of inappropriate antidiuretic hormone secretion.[41]

Anticholinergics

Anticholinergic agents, in the form of alkaloids derived from the Solanaceae family,[42] are the oldest medication in use for the treatment of PD after their antiparkinsonian effects were first described by Leopold Ordenstein in 1868.[43] Since then, anticholinergic agents remained the only pharmacological treatment option for PD for almost a century until the introduction of levodopa and amantadine in the 1960's.[44]

Although the use of anticholinergics for the treatment of motor symptoms in PD has declined due to the increasing use of levodopa and other drugs,[45] they are still the first-line treatment for bladder dysfunction, the commonest autonomic disorder in PD which also tends to be non-responsive to levodopa.[46-47]

As anticholinergic drugs are often prescribed for the treatment of sialorrhea in patients with cerebral palsy, sublingual atropine has been investigated for potential use in treating sialorrhea in PD patients.[48,49] While sublingual atropine did result in an amelioration in sialorrhea, 3 out of the 7 study subjects experienced adverse effects, mainly of cognitive nature.[49] Due to such results, the use of atropine in the management of sialorrhea in PD patients is only recommended by the NICE guidelines if the "risk of cognitive adverse effects is thought to be minimal".[50-51]

In 2018, a case report was published where a 75-year-old gentleman with a known case of PD developed psychosis and delirium following the commencement of sublingual atropine.[50]

Indeed, although studies have shown anticholinergic agents to be more effective in treating motor symptoms in PD than placebo, their adverse effects, especially on cognitive function in PD patients - who due to the cholinergic dysfunction associated with their disease makes them more prone to anticholinergic effects – greatly limit their use.[17,52]

Deep Brain Stimulation

Deep brain stimulation of the subthalamic nucleus is the preferred surgical treatment for advanced PD, especially in those who respond to pharmacological treatment but have motor fluctuations. While in general, the quality of life of the patients undergoing this surgery increases as the symptoms are improved, side effects and complications do exist. Pneumonia (amongst other infections) and intracranial haemorrhage are the commonest complications associated with the surgical procedure itself, albeit the frequency of such complications is relatively low, occurring at a rate of 0.6% and 2.2%, respectively. Furthermore, the mortality rate and the rate of permanent surgical morbidity were found to be 0.4% and 1%, respectively.[53] Adverse effects to the stimulation are possible but are often reversible and can be alleviated by adjusting the kind of stimulation.[54] In most cases, the incidence of complications can be reduced or prevented by carefully selecting the patients for surgery which are the most likely to benefit from such a procedure while having a low risk profile vis-à-vis surgical complications.[55]

Cannabis ... The Future of PD Treatment?

A 2017 report on the health benefits of cannabis "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research" carried out by the "National Academies of Sciences, Engineering and Medicine" concluded that while there is conclusive or substantial evidence that cannabis/cannabinoids are effective for the treatment of chronic pain in adults and as antiemetics to name a few, there is insufficient evidence to prove or disclaim the effectiveness of cannabis or cannabinoids in the treatment of PD.[56] In this paper, we will be reviewing the current state of evidence that exists for and against the use of this drug for the treatment of PD and what led the "National Academies of Science, Engineering and Medicine" to come to this conclusion.

Cannabis contains over 100 different phytocannabinoids – compounds occuring in plants that interact the endocannabinoid system. The main phytocannabinoids responsible for the therapeutic effects of cannabis are Δ^9-tetrahydrocannabidiol (THC) which is the primary psychoactive component of cannabis and cannabidiol (CBD), a non-psychoactive compound that has been shown to possess anti-inflammatory, anti-psychotic, neuroprotective and analgesic properties.[57,58] These compounds interact with the endocannabinoid system – a system composed of the cannabinoid type 1 and 2 receptors (CB_1 and CB_2 respectively), the endogenous ligands that bind to these receptors, known as endocannabinoids, and the proteins that are responsible for the syntheses, reuptake and degradation of these ligands.[59]

While CB_1 receptors are expressed both in the central nervous system and the periphery, they are most abundant in the former, especially in

the structures that are related to movement i.e. basal ganglia, prefrontal cortex, hippocampus and cerebellum.[60] Indeed, CB1 receptors are the most widely distributed G-protein-coupled receptor in the CNS.[61]

Several studies have reported an upregulation of CB_1 receptors in the basal ganglia as a response to the depletion in dopamine typically seen in PD; highlighting the possibility of employing cannabinoids as therapeutic agents in the treatment of the motor symptoms associated with PD.[62]

Basal ganglia are the subcortical nuclei which, in connection with the brainstem, thalamus and motor cortex, they modulate voluntary motor movements through two pathways: (1) the direct pathway which is mediated by D1 receptors and promotes movement, and (2) the indirect pathway which is mediated by D2 receptors which inhibits movement.[63–65] Normally, these two pathways are in balance with each other; this balance is lost in PD as the depletion of dopamine in the striatum causes inhibition of the direct pathway and activation of the indirect pathway. This loss in balance results in an over-inhibition of the thalamus leading to an excessive inhibition of motor symptoms which in turn results in parkinsonian motor features.[63–66]

Via the CB_1 receptors located at the level of the presynaptic region of the glutamatergic terminal, cannabinoids can reduce the glutamatergic overactivity that results from the change in the balance between the direct and indirect pathways.[67]

CB2 receptors levels are usually very low in the healthy brain but increase in cases of injury or inflammation. They occur mostly in the periphery such as in the thymus and spleen.[67–69]

Pertwee argues that CBD antagonises the action of CB_1 and CB_2 receptor agonists, acting as an inverse agonist of these receptors [70]. Some of the latest studies have suggested that CBD acts as a non-competitive negative allosteric modulator of both CB_1 and CB_2 receptors.[71,72] Some of the effects of CBD seem to result from the increase in the anandamide levels induced by the aforementioned cannabinoid as it inhibits its enzymatic hydrolysis and uptake.[73]

Mitochondrial dysfunctions, such as those due to the alterations in mitochondrial DNA, bioenergetic defects, reactive oxygen species generation and dysfunctional calcium homeostasis have all been associated with the mechanisms underlying the neuronal death in PD.[74] Interestingly, studies have found that CBD acts on the mitochondria by increasing the activity of the mitochondrial complexes I, II, II-III and IV in rats. CBD has also been reported to reverse the epigenetic modifications of mitochondrial DNA induced by iron overload in rats. Iron overload induces pathological changes that resemble neurodegenerative disorders like PD.[75,76]

As already mentioned, levodopa, while effective in treating the motor symptoms of PD, it is ineffective in the treatment of non-motor symptoms, which can have as much of devastating effects on the patient as much as the motor symptoms. A 2009 study found that treating PD patients with CBD for 4 weeks resulted in a decrease in the psychotic symptoms without affecting the motor function or causing adverse effects.[77]

A randomised, double-blind placebo-controlled, crossover study involving five participants showed a significant reduction in levodopa-induced dyskinesia and in the symptoms associated with rapid eye movement sleep behaviour disorder in those

treated with nabilone (a synthetic cannabinoid similar to THC) when compared with those taking the placebo.[78]

Another 2014 study by Chagas *et al.* also that treating PD patients with CBD results in an improvement in their quality of life, even if their symptoms are not ameliorated. This finding has been suggested that it might be due to the anxiolytic, antipsychotic and antidepressant effects that they exert.[79] The same finding has been reported in another study in which participants treated with 75 mg or 300 mg daily doses of CBD failed to report any change in PD symptoms as assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) but they did report an improvement in the quality of life as assessed using the Parkinson's Disease Questionnaire (PDQ-39).[80]

In a 2015 study based on self-administered surveys found that more than 70% of PD patients that made use of cannabis that were surveyed reported improvement in mood and sleep.[81]

Although these studies herald an opportunity for the treatment of PD with levodopa in conjunction with CBD to control both the motor and non-motor symptoms, they were unfortunately underpowered and therefore the samples are not representative of the general PD population. Furthermore, the study carried out by Lotan *et al.* was open-label, increasing the risk of bias in the results obtained one must therefore be cautious when analysing such results.

Other studies have failed to show optimistic results regarding the use of cannabis in treating PD. For instance, in studies carried out by Carroll *et al.* and Mesnage *et al.* involving seventeen and eight participants respectively failed to show any significant improvement in motor or non-motor symptoms when treated with Cannador and Rimonabant, respectively.[82-83]

While back in 1999, the Institute of Medicine declared the short-term use of cannabinoids to be safe, little has been done to determine the safety of cannabinoids in the long-term use.[84] If the cannabinoids are administered by smoking the cannabis plant, certain side effects related to the act of smoking can be expected, such as chronic bronchitis or other respiratory diseases.[85]

While many studies have shown that CBD has an antipsychotic effect,[84] Udow *et al.* argue that since patients with PD have an inherent risk of psychosis, they are more likely of developing psychosis if they are subjected to cannabinoids. Udow *et al.* presented a case study where a 70-year old woman with a 12-year history of PD developed an exacerbation of psychosis following the ingestion of nabilone.[86]

This difference in the literature is due to the generalisation made by Udow *et al.* where they attribute the occurrence of psychosis with cannabinoids in general. In their same paper, they specify that the 70-year old lady had exacerbation following the ingestion of nabilone – a synthetic chemical that mimics THC, the psychoactive agent in cannabis which studies have found to cause psychotic symptoms. On the other hand, the antipsychotic effect has only been reported in CBD, a non-psychoactive agent. Hence, one must not make the mistake of generalising all the cannabinoids together, as there can be major differences pharmacological action between one cannabidiol and another.

Conclusion

In agreement with the 2017 report by the "National Academies of Science, Engineering and Medicine" the current evidence in favour of cannabinoids for the treatment of PD is of low quality and inconclusive. Further studies and clinical trials involving larger sample sizes and better methods are needed to reach a conclusion on whether cannabidiols are the future of PD treatment or not.

References

1. Lee A, Gilbert RM. Epidemiology of Parkinson Disease. *Neurol Clin* 2016;34(4):955–65.
2. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem* 2016 Oct;139 Suppl 1:318-324.
3. Broen MPG, Narayen NE, Kuijf ML, Dissanayaka NNW, Leentjens AFG. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord* 2016 Aug;31(8):1125-33.
4. von Campenhausen S, Bornschein B, Wick R, Bötzel K, Sampaio C, Poewe W, et al. Prevalence and incidence of Parkinson's disease in Europe. *Eur Neuropsychopharmacol* 2005;15(4):473–90.
5. Parkinson J. An Essay on the Shaking Palsy. *J Neuropsychiatry Clin Neurosci* 2002 May 1;14(2):223–36.
6. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 2009 May;8(5):464-74.
7. Singh N, Pillay V, Choonara YE. Advances in the treatment of Parkinson's disease. Prog Neurobiol. 2007 Jan;81(1):29-44.
8. Zuardi AW. History of cannabis as a medicine: A review. *Braz J Psychiatry* 2006 Jun;28(2):153-7.
9. Ko GD, Bober SL, Mindra S, Moreau JM. Medical cannabis – The Canadian perspective. *J Pain Res* 2016 Sep 30;9:735-744.
10. Andreou E. House passes law on medical cannabis. CyprusMail Online [Internet]. 2019 Feb 15; Available from: https://cyprus-mail.com/2019/02/15/house-passes-law-on-medical-cannabis/
11. Pace M. Malta has officially legalised medical cannabis. maltatoday [Internet]. 2018 Mar 27; Available from: https://www.maltatoday.com.mt/news/national/85616/malta_has_officially_legalised_medical_cannabis#.XHLijYhKjIU
12. BBC. Medicinal cannabis products to be legalised. 2018 Jul 26; Available from: https://www.bbc.com/news/health-44968386
13. Bega D, Simuni T, Okun MS, Chen X, Schmidt P. Medicinal Cannabis for Parkinson's Disease: Practices, Beliefs, and Attitudes Among Providers at National Parkinson Foundation Centers of Excellence. *Mov Disord Clin Pract* 2017;4: 90-95.
14. Olanow CW, Agid Y, Mizuno Y, Albanese A, Bonucelli U, Damier P, et al. Levodopa in the treatment of Parkinson's disease: Current controversies. *Mov Disord* 2004 Sep;19(9):997-1005.
15. Gershanik O, Emre M, Bernhard G, Sauer D. Efficacy and safety of levodopa with entacapone in Parkinson's disease patients suboptimally controlled with levodopa alone, in daily clinical practice : an international , multicentre , open-label study. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:963–71.
16. Joint Formulary Committee. British National Formulary. 76th ed. London, United Kingdom: Pharmaceutical Press; 2018.
17. Crispo JAG, Willis AW, Thibault DP, Fortin Y, Hays D, Mcnair DS, et al. Associations between Anticholinergic Burden and Adverse Health Outcomes in Parkinson Disease. *PLoS One* 2016 Mar 3;11(3):e0150621.

18. Waters CH, Kurth M, Shulman LM. Tolcapone in stable Parkinson's disease : Efficacy and safety of long-term treatment. *Neurology* 1997 Sep;49(3):665-71.

19. Assal F, Spahr L, Hadengue A, Rubbici-Brandt L, Burkhard PR. Tolcapone and fulminant hepatitis. *Lancet* 1998 Sep 19;352(9132):958.

20. Olanow CW, and the Tasmar Advisory Panel. Tolcapone and Hepatotoxic Effects. *Arch Neurol* 2000;57(2):263–7.

21. Olanow CW, Watkins PB. Tolcapone: An efficacy and safety review (2007). *Clin Neuropharmacol* 2007 Sep-Oct;30(5):287-94.

22. Stocchi F, Torti M, Fossati C. Advances in dopamine receptor agonists for the treatment of Parkinson's disease. *Expert Opin Pharmacother* 2016 Oct;17(14):1889-902.

23. Jenner P. Pharmacology of dopamine agonists in the treatment of Parkinson's disease. *Neurology* 2002 Feb 1;58(suppl 1):S1 LP-S8.

24. Hubble JP. Long-term studies of dopamine agonists. *Neurology* 2002 Feb 1;58(suppl 1):S42 LP-50.

25. Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE. Frequency of New-Onset Pathologic Compulsive Gambling or Hypersexuality After Drug Treatment of Idiopathic Parkinson Disease. *Mayo Clin Proc* 2009 Apr;84(4):310-6.

26. Grady MM, Stahl SM. Practical guide for prescribing MAOIs: debunking myths and removing barriers. *CNS Spectr* 2012;17(1):2–10.

27. Thomas A. Iacono D. Luciano AL. Armellino K. Di Iorio A. Onofrj M. Duration of amantadine. *J Neurol Neurosurg Psychiatry* 2004;75(1):141–3.

28. Saint-Cyr JA, Trépanier LL. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2000;15(5):873–8.

29. Hubsher G, Haider M, Okun MS. Amantadine: The journey from fighting flu to treating Parkinson disease. *Neurology* 2012;78(14):1096–9.

30. Jahangirvand A, Rajput A. Early Amantadine Treatment Does Not Delay Onset of Dyskinesias in Parkinson's Disease. *Neurology* 2013 Feb 12;80(7 Supplement):P02.080 LP-P02.080.

31. Crosby NJ DK, Clarke CE. Amantadine in Parkinson's disease. *Cochrane Database Syst Rev* 2003;(1).

32. Weintraub D, Sohr M, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study. *Ann Neurol* 2010 Dec 1;68(6):963–8.

33. Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofrj M. Pathological gambling in Parkinson disease is reduced by amantadine. *Ann Neurol* 2010 Sep 1;68(3):400–4.

34. Ghaffariyeh A, Honarpisheh N. Amantadine-associated corneal edema. *Park Relat Disord* 2010 Jul;16(6):427.

35. Kubo S, Iwatake A, Ebihara N, Murakami A, Hattori N. Visual impairment in Parkinson's disease treated with amantadine: Case report and review of the literature. *Park Relat Disord* 2008;14(2):166-9.

36. Fraunfelder FT, Meyer SM. Amantadine and Corneal Deposits. *Am J Ophthalmol* 1990 Jul 1;110(1):96–7.

37. Boyd JT, Silverman DA. Case Report Amantadine-Induced Patulous Eustachian Tubes in Parkinson' s Disease. *Case Rep Otolaryngol* 2013; 2013: 426413.

38. Kataoka H, Ueno S. Dropped head associated with amantadine in parkinson disease. *Clin Neuropharmacol* 2011;34(1):48–9.

39. Marxreiter F, Winkler J, Uhl M, MadŽar D. A Case Report of Severe Delirium after Amantadine Withdrawal. *Case Rep Neurol* 2017; Mar 20;9(1):44-8.

40. Kocaş C, Türkmen Y, Çetinkal G, Dołan SM. Right ventricular outflow tract tachycardia after an initial dose of amantadine. *Turk Kardiyol Dern Ars* 2015; Jul;43(5):472-4.

41. Alonso Navarro H, Sánz-Aiz A, Izquierdo L, Jiménez Jiménez FJ. Syndrome of inappropriate antidiuretic hormone secretion possibly associated with amantadine therapy in Parkinson disease. *Clin Neuropharmacol* 2009;32(3):167–8.

42. Adler CH. Amantaine and anticholinergics. In: Factor S, Weiner W, editors. Parkinson's disease: Diagnosis & clinical management. 2nd ed. New York, NY: Demos Medical Publishing; 2007. p. 491–7.

43. Lehmann HC, Hartung HP, Kieseier BC. Leopold Ordenstein: On paralysis agitans and multiple sclerosis. *Mult Scler* 2007;13(9):1195–9.

44. Kim HJ, Jeon BS, Jenner P. Hallmarks of Treatment Aspects: Parkinson's Disease Throughout Centuries Including L-Dopa. 1st ed. Vol. 132, International Review of Neurobiology. Elsevier Inc.; 2017.

45. Brocks DR. Anticholinergic drugs used in Parkinson's disease: An overlooked class of drugs from a pharmacokinetic perspective. *J Pharm Pharm Sci* 1999;2(2):39–46.

46. Nagao T, Tateno F, Yano M, Tsuyusaki Y, Yamamoto T, Aiba Y, et al. Bladder function of patients with Parkinson's disease. *Int J Urol* 2014;21(7):638–46.

47. Sakakibara R, Tateno F, Kishi M, Tsuyuzaki Y, Uchiyama T, Yamamoto T. Pathophysiology of bladder dysfunction in Parkinson's disease. *Neurobiol Dis* 2012;46(3):565–71.

48. Chou KL, Evatt M, Hinson V, Kompoliti K. Sialorrhea in Parkinson's disease: A review. *Mov Disord* 2007 Dec;22(16):2306-13.

49. Hyson HC, Johnson AM, Jog MS. Sublingual Atropine for sialorrhea secondary to parkinsonism: A pilot study. *Mov Disord* 2002 Nov 1;17(6):1318–20.

50. Ferris A, Mohamed B, Thomas C. Eye drop psychosis in parkinson's disease: A cautionary tale. *Prog Neurol Psychiatry* 2018;22: 11-14.

51. National Institute for Health and Care Excellence (NICE). Parkinson's disease in adults. NICE guidelines NG71. London: NICE, 2017.

52. Katzenschlager R, Sampaio C, Costa J, Lees A. Anticholinergics for symptomatic management of Parkinson´s disease. *Cochrane Database Syst Rev* 2003;(2):CD003735

53. Tanei T, Kajita Y, Kaneoke Y, Takebayashi S, Nakatsubo D, Wakabayashi T. Staged bilateral deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Acta Neurochir (Wien)* 2009 Jun;151(6):589-94.

54. National Academies of Sciences Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Researcho Title. 1st ed. National Academies Press; 2017.

55. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Brazilian J Psychiatry* 2008;30:271–80.

56. Babayeva M, Assefa H, Basu P, Chumki S, Loewy Z. Marijuana Compounds: A Nonconventional Approach to Parkinson's Disease Therapy. *Parkinsons Dis* 2016;2016.

57. Scotter EL, Abood ME, Glass M. The endocannabinoid system as a target for the treatment of neurodegenerative disease. *Br J Pharmacol* 2010;160(3):480–98.

58. Piomelli D. The molecular logic of endocannabinoid signalling. *Nat Rev Neurosci* 2003 Nov;4:873.

59. Grotenhermen F, Müller-Vahl K. The therapeutic potential of cannabis and cannabinoids. *Dtsch Arztebl Int* 2012 Jul;109(29–30):495–501.

60. Giacoppo S, Molino G, Galuppo M, Mazzon PBE. Cannabinoids: New promising agents in the treatment of neurological diseases. *Molecules* 2014;19(11):18781-816.

61. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, et al. Pathophysiology of the basal ganglia in Parkinson's disease. *Trends Neurosci* 2000 Oct;23:S8–19.

62. Stocco A, Lebiere C, Anderson JR. Conditional routing of information to the cortex: a model of the basal ganglia's role in cognitive coordination. *Psychol Rev* 2010 Apr;117(2):541–74.

63. Blandini F, Nappi G, Tassorelli C, Martignoni E. Functional changes of the basal ganglia circuitry in Parkinson's disease. *Prog Neurobiol* 2000;62(1):63–88.

64. More SV, Choi D-K. Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. *Mol Neurodegener* 2015 Apr;10:17.

65. Brotchie JM. CB1 cannabinoid receptor signalling in Parkinson's disease. *Curr Opin Pharmacol* 2003;3(1):54–61.

66. Maresz K, Carrier EJ, Ponomarev ED, Hillard CJ, Dittel BN. Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli. *J Neurochem* 2005 Oct;95(2):437–45.

67. Carlisle SJ, Marciano-Cabral F, Staab A, Ludwick C, Cabral GA. Differential expression of the CB2 cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation. *Int Immunopharmacol* 2002;2(1):69–82.

68. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. *Br J Pharmacol* 2008 Jan;153(2):199–215.

69. Laprairie RB, Bagher AM, Kelly MEM, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *Br J Pharmacol* 2015 Oct;172(20):4790–805.

70. Martínez-Pinilla E, Varani K, Reyes-Resina I, Angelats E, Vincenzi F, Ferreiro-Vera C, et al. Binding and Signaling Studies Disclose a Potential Allosteric Site for Cannabidiol in Cannabinoid CB2 Receptors. *Front Pharmacol* 2017;8:744.

71. Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012 Mar;2:e94.

72. Ammal Kaidery N, Thomas B. Current perspective of mitochondrial biology in Parkinson's disease. *Neurochem Int* 2018;117:91–113.

73. da Silva VK, de Freitas BS, Dornelles VC, Kist LW, Bogo MR, Silva MC, et al. Novel insights into mitochondrial molecular targets of iron-induced neurodegeneration: Reversal by cannabidiol. *Brain Res Bull* 2018;139:1–8.

74. Valvassori SS, Bavaresco D V, Scaini G, Varela RB, Streck EL, Chagas MH, et al. Acute and chronic administration of cannabidiol increases mitochondrial complex and creatine kinase activity in the rat brain. *Brazilian J Psychiatry* 2013;35:380–6.

75. Zuardi AW, Crippa JAS, Hallak JEC, Pinto JP, Chagas MHN, Rodrigues GGR, et al. Cannabidiol for the treatment of psychosis in Parkinsons disease. *J Psychopharmacol* 2009;23(8):979–83.

76. Chagas MHN, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sobreira-Neto MA, Sobreira ET, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: A case series. *J Clin Pharm Ther* 2014;39(5):564-6.

77. Chagas MHN, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *J Psychopharmacol* 2014;28(11):1088–92.

78. 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. *Clin Neuropharmacol* 2014;37(2):41–4.

79. Finseth TA, Hedeman JL, Brown RP, Johnson KI, Binder MS, Kluger BM. Self-reported efficacy of cannabis and other complementary medicine modalities by Parkinson's disease patients in Colorado. *Evid Based Complement Altern Med* 2015;1-6.

80. Mesnage, V; Houeto, JL; Bonnet, AM, Clavier, I; Arnulf I, Cattelin, F; Le Fur, G; Damier, P; Welter, ML AY. Neurokinin B, neurotensin, and cannabinoid receptor antagonists and Parkinson disease. *Clin Neuropharmacol* 2004;27(3):108–10.

81. Carroll CB, Bain PO, Teare L, Liu X, Joint C, Wroath C, et al. Cannabis for dyskinesia in Parkinson disease: A randomized double-blind crossover study. *Neurology* 2004;63(7):1245–50.

82. Degenhardt L, Hall WD. The adverse effects of cannabinoids: implications for use of medical marijuana. *CMAJ* 2008 Jun;178(13):1685–6.

83. Van Dam NT, Earleywine M. Pulmonary function in cannabis users: Support for a clinical trial of the vaporizer. *Int J Drug Policy* 2010;21(6):511–3.

84. Udow SJ, Freitas ME, Fox SH, Lang AE. Exacerbation of psychosis triggered by a synthetic cannabinoid in a 70-year-old woman with Parkinson disease. *CMAJ* 2018 Jan;190(2):E50—E52.