

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

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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.

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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 derivatives 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 tachycardia⁴⁰ 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 sialorrhoea in patients with cerebral palsy, sublingual atropine has been investigated for potential use in treating sialorrhoea in PD patients.^{48,49} While sublingual atropine did result in an amelioration in sialorrhoea, 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 sialorrhoea 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 occurring in plants that interact the endocannabinoid system. The main phytocannabinoids responsible for the therapeutic effects of cannabis are Δ^9 -tetrahydrocannabinol (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 (CB₁ and CB₂ 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 CB₁ 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 CB₁ 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 CB₁ 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 CB₁ and CB₂ receptor agonists, acting as an inverse agonist of these receptors⁷⁰. Some of the latest studies have suggested that CBD acts as a non-competitive negative allosteric modulator of both CB₁ and CB₂ 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.

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