Commentary Article

Sorting through the weeds: a commentary on the use of cannabinoids in Parkinson's

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INTRODUCTION

Background: Parkinson's disease (PD) is a neurodegenerative disorder with growing prevalence, age-standardised death rates and disability. Recent expansions in cannabis legalization have revived interest in therapeutic applications of medical cannabis and its derivatives (MC) in PD. Our team previously conducted a systematic review and meta-analysis on the use of MC in PD patients to determine its effect on motor function and its safety profile.

Methods: In this commentary we review our original findings and contextualize them considering newly published evidence.

Results: Our original study included 15 studies, including 6 RCTs, of which 12/15 (80%) mention concomitant treatment with anti-parkinsonian medications, most commonly levodopa. Treatment duration in intervention-based studies ranged from single-dose administration to 6 weeks. RCTs most commonly measured motor effect using the Unified Parkinson Disease Rating Scale (UPDRS) motor score while observational studies mostly used patient self-reporting. Although most of the observational data without appropriate controls favored the intervention, the RCTs demonstrated no significant motor symptom improvement. A meta-analysis of 3 RCTs (n = 83) did not demonstrate statistically significant improvement in UPDRS motor scores (MD -0.21, 95% CI -4.15 to 3.72; p = 0.92). A single study reported improvement in dyskinesia ($p < 0.05$). The intervention was generally well tolerated. None of the included studies had a low risk of bias. One new open-label dose escalation study has been published since the time of our original review. Although its findings are inconclusive, the authors suggest potential for improvement of UPDRS motor scores with MC (mean decrease 24.7%, p = 0.004).

Conclusion: Although observational studies establish subjective symptom alleviation and interest in MC among PD patients, the poor quality of existing evidence does not support its integration into clinical practice for motor symptom treatment. Future investigations using standardized tools such as the UPDRS should look at tolerance and the role of MC as an adjuvant treatment to standard PD therapies among participants with more variable disease duration to determine the effectiveness MC for the treatment of motor PD symptoms.

Keywords: Parkinson's disease; medical cannabis; cannabinoids; cannabidiol; adjuvant therapy

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disorder. Among all the neurological disorders examined in a 2015 Global Burden of Disease study, PD emerged as the only one with increasing age-standardized rates of deaths, prevalence and disability.1 In fact, the prevalence of PD more than doubled between 1990 (2.5 million) and 2016 (6.1 million) worldwide, with an age-standardized prevalence rate increase of 21.7% over the same period.2

The disease is characterized by the cardinal motor symptoms of bradykinesia, rigidity, postural instability and resting tremor, which are often accompanied by non-motor symptoms including sleep disturbances, cognitive changes, depression, pain and autonomic dysfunction, among others. These motor symptoms are caused by the loss of dopaminergic neurons in the substantia nigra pars compacta which leads to depletion of dopamine in the striatum.3

Standard PD treatment involves using dopamine precursors such as levodopa to correct the deficiency. However, with chronic use, as more neurons are lost with further disease progression, the efficacy of levodopa diminishes and patients experience dyskinesia and motor fluctuations, termed levodopa-induced dyskinesia (LID).3 More recently, research has implicated non-dopaminergic systems such as the endocannabinoid system (ECS) in PD, which has garnered interest as a potential new target given the limitations associated with standard PD treatment.

A ROLE FOR CANNABINOIDS?

The ECS is comprised of endo cannabinoids that act at cannabinoid receptor type 1 (CB1) receptors to modulate neurotransmission involved in motor function, especially within the basal ganglia.4 Over activity of the ECS has been shown both in PD patients5–7 and in animal models7 of the disease. As such, the ECS was extensively explored as a target for pharmacological intervention in PD.8 There is a large body of pre-clinical evidence demonstrating the beneficial effects of cannabinoids with respect to delaying disease progression9, through neuroprotective10,11 and anti-inflammatory9 properties, and relief of LID12 and motor symptoms9 such as tremor13 and bradykinesia.14 Cannabinoid therapies show promise both as adjunctive treatments to levodopa, and as possible monotherapies.14 However, although pre-clinical studies show promise, little is known about how these results translate to clinical applications.15

In the last decade, with expansions in the legalization of cannabis worldwide, especially in Canada, the United States and Israel, there has been renewed interest in its therapeutic applications for neurological disorders.16 A 2015 survey of neurologists at PD centers in the United States reported that 95% of respondents had been asked by their patients to prescribe cannabis within the last year.17 Importantly, the same study also found that while 80% of practitioners had PD patients who used cannabis, only 23% had any education of its applicability on PD.17 However, in spite of patient interest, a more recent survey among PD patients found that most respondents did not use cannabis, primarily citing lack of scientific evidence supporting efficacy (60%) and a fear of its side effect profile (35%) as reasons.18 Despite these gaps in the literature, many patients around the world do report self-medicating with cannabis and its derivatives for a variety of symptoms, including both motor and non-motor symptoms of PD.

A recent systematic review and meta-Analysis19 done by our team found several previous systematic reviews that evaluated the roles of cannabinoids in neurodegenerative and movement disorders more generally,20–22 rather than in PD alone. One recent systematic review23 that did focus on cannabis for PD evaluated efficacy more broadly by including non-motor

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Citation: *Thanabalasingam SJ (2021) Sorting through the weeds: a commentary on the use of cannabinoids in Parkinson's. J Clin Psychiatr Neurosc . 4(6).*

Received date: *July 13, 2021*; **Accepted date:** *October 13, 2021*; **Published date:** *October 25, 2021*

symptoms, and offered a narrative summary of studies' results without combining outcome data. As such, we sought to investigate efficacy and safety more specifically by examining the following two questions.

(1) What is the direction and magnitude of effect of medical cannabis (MC) in alleviating motor symptoms and dyskinesia in adult PD patients?

(2) What side effects and adverse events are associated with the use of cannabis and its derivatives?

We conducted a systematic review and meta-analysis of randomized controlled trials and observational studies examining the use of cannabis and its derivatives for the treatment of motor symptoms in adults with PD. 19 Observational studies included both non-randomized interventional studies and questionnaire-based studies. Electronic searches of PsychInfo, EMBASE, MEDLINE, and Evidence-Based Medicine Reviews - Cochrane Central Register of Controlled Trials were performed from the date of their inception to early December 2020. We created a forest plot for the outcome of motor function efficacy calculating a mean difference and its 95% confidence interval (CI) using a random effects model to account for clinical heterogeneity of the meta-analyzed studies. Primary outcomes were change in motor function using the Unified Parkinson Disease Rating Scale (UPDRS) III motor score and change in dyskinesia using the UPDRS IV sub-score. Secondary outcomes included adverse events and side effects. Limiting the scope of our study to efficacy with respect to motor symptoms meant that safety data from studies that examined non-motor symptoms alone may not have been captured. Risk of bias was assessed at the study level using the Cochrane Risk of Bias Tool for RCTs24 and crossover trials25 and using the Modified Newcastle-Ottawa Criteria for Cross-Sectional Studies26 for uncontrolled observational studies.

RESULTS

We analyzed 15 studies (6 RCTs and 9 observational studies) including 3079 patients for the primary outcome of motor function efficacy. Six studies (40%) were conducted in Europe, three (20%) in the Middle East, four (27%) in South America, and two (13%) in the United States. Twelve studies (80%) mentioned concomitant treatment with antiparkinsonian medications, most commonly levodopa, but a minority (33%) of these provide any details about the drugs used. Among studies investigating the primary outcome the mean age was 68.1 years, the mean PD duration was 10.5 years, 43% were female and only 7 studies reported the Hoehn and Yahr (H&Y) stage (mean27–29 H&Y 1.78, median30–32 H&Y 2.2). Treatment duration in the intervention-based studies ranged from single dose administration to 6 weeks, while questionnaire-based studies ranged from approximately 2 months to 1.5 years of use.

Although observational data without appropriate controls had effect estimates favoring the intervention, the RCTs demonstrated no significant motor symptom improvement overall. A meta-analysis of 3 RCTs, which comprised 83 patients, did not demonstrate a statistically significant improvement in UPDRS III score variation (MD -0.21, 95% CI -4.15 to 3.72; $p = 0.92$) with MC use. Only one randomized-controlled crossover study27 (12%) reported statistically significant improvement in dyskinesia ($p < 0.05$). The intervention was generally well tolerated, with the most commonly reported side effects being fatigue, unsteadiness and dizziness. These safety data generally relied on patient self-report and assessed side effects over relatively short (≤ 4 weeks) durations of use. All RCTs had a high risk of bias and none of the observational studies achieved the minimum score to be considered good with respect to risk of bias.

NEW EVIDENCE

Since our published review, a new open-label dose escalation study by Leehey et al.33 is the first to study the effects of relatively high dose of purified oral cannabidiol (CBD) (~20 mg/kg/day) in the PD population. They included 13 participants with a similar mean age (68.2 vs. 68.1 years) and a shorter disease duration (6.1 vs. 10.5 years) than noted in our systematic review. The most commonly reported adverse effects were including diarrhea (85%), somnolence (69%) and fatigue (62%). Additionally, they found a transient cholestatic pattern of liver enzyme elevation associated with the high dose used in the study in 5/13 (39%) study participants. The authors highlight that although no conclusions can be drawn about efficacy given the open-label nature, their assessment does suggest potential for improvement of UPDRS motor scores with MC (mean decrease 24.7%, $p = 0.004$). Study strengths included rigorous outcome assessment using standardized tools and objective safety endpoints, vigilance in documenting participants' levodopa daily dose equivalents (LE) of dopaminergic medications, and situating the findings in the context of prior studies34,35 that used the same purified oral CBD formulation. The study was primarily limited by the small sample size, short study duration and the biases inherent to an open label study design.

RECOMMENDATIONS

Some observational studies show subjective symptom alleviation and interest among PD patients in using MC. This is limited by poor quality of evidence often lacking an appropriate comparator group. Given the current landscape of the evidence, we cannot recommend changing clinical practice to incorporate cannabis and its derivatives in the treatment of PD motor symptoms at this time. Before recommendations can be re-evaluated, we require placebo-controlled investigations using much larger sample sizes, over longer intervention durations. As product doses, formulations and routes of administration available to patients are highly variable, determining the effects of varying composition, doses and routes is prudent. Future investigations should make consistent use of standardized tools such as the UPDRS and move away from patient self-reports of improvement for outcome measurement given the latter's inherent risk of bias. These studies should additionally look at tolerance and the role of MC as an adjuvant treatment to standard PD therapies by documenting LE among participants with more variable disease duration to determine the effectiveness MC for the treatment of motor PD symptoms.

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