ORIGINAL SCIENTIFIC ARTICLES

Use of Cannabis in the Improvement in the Unified Parkinson's Disease Rating Scale Score of Parkinson's Disease: A Meta Analysis

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BACKGROUND
Cannabis, the source of Δ9-tetrahydrocannabinol (THC), the primary psychotropic compound, and cannabidiol (CBD), a nonpsychoactive chemical with potential therapeutic properties, has been widely used as a psychoactive drug, medicinal drug, or industrial hemp. Cannabinoids exert their effect in the brain mainly by interacting with two types of receptors: CB1 and CB2 receptors, which are currently being studied for its possible therapeutic effects for the symptomatic treatment of Parkinson's Disease.

METHODOLOGY
Databases searched were PubMed via National Center for biotechnology Information, CINAHL, Medline, Academic Search, Biomedical Reference collection, via EBSCOhost, and Cochrane Library. Queries were sent to local institutions for unpublished studies compatible with the criteria for study eligibility. Participants' characteristics, study design, intervention features, outcome variables, reported effects, and study quality were retrieved. Random effects model was used because heterogeneity was significant.

RESULTS
The analysis of the four clinical trials included in the study showed that *Cannabis* and its derivatives' effects on the mean motor UPDRS showed statistically significant decrease.

CONCLUSION
Cannabis and its derivatives may have an effect in the short-term symptomatic treatment of Parkinson's Disease, although controlled studies with larger samples must be done before any conclusions may be made.

INTRODUCTION

Cannabis is a plant that is the source of over 60 pharmacologically active compounds or phytocannabinoids, including Δ9-tetrahydrocannabinol (THC), the primary psychotropic compound, and cannabidiol (CBD), a nonpsychoactive chemical with potential therapeutic properties.[1] Cannabis has three recognized species, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis has been widely used as a psychoactive drug, medicinal drug, or industrial hemp. Its legality for use still varies from country to country as a result of the agreement about Indian hemp in the International Opium Convention back in 1925[1], as well as its supposed addictive effect as a psychoactive drug on its users.

The future of Cannabis as a medical drug appear promising as the number of scientific studies has expanded notably over the past few decades. Currently, there is still no large-scale human trial which would unequivocally confirm that medical *Cannabis* is effective for medicinal purposes, or more effective than other medicines on the market.[2] While the most popular fields of research focus on cannabinoids as a treatment for pain control, cancer, Post-traumatic Stress Disorder, and

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pediatric epilepsy, an emerging possible indication for Cannabis may be for movement disorders.

Cannabidiol (CBD) is one of the main components of Cannabis sativa, but is not involved in its psychomimetic effects. Pharmacological studies on CBD have shown that the substance has a wide spectrum of action with different effects on different systems.[3] Cannabinoids exert their effect mainly by interacting with two types of receptors: CB1 and CB2 receptors. CB1 receptors are located mainly on neurons and glial cells in the brain and in several other organs in the body, while CB2 receptors are found mainly on immune cells, and are less common in the brain than CB1 receptors.[4] CBD acts on other brain signaling systems (e.g., serotonin receptors), and it is these actions that are thought to be important to its therapeutic effects.[5]

The neuroprotective properties of CBD have been under increasing scientific scrutiny in the context of neurodegenerative diseases, including Huntington's disease, Alzheimer's disease, and Parkinson's disease.[6] Cannabinoids, through the brain's endocannabinoid receptors, can decrease the activity of the output system of dopaminergic neurons downstream from the striatum through the stimulation of gamma-aminobutyric acid (GABA)ergic receptors localized on striatopallidal neurons.[7] This study aims to determine whether the use of Cannabis or its derivatives, along with the standard of care, will result in a reduction of the total motor UPDRS score of patients with Parkinson's Disease.

RATIONALE

The treatment of Parkinson disease (PD), which is characterized by the selective degeneration of mesostriatal dopaminergic neurons, is based on the administration of levodopa and related compounds, allowing normal brain dopaminergic transmission to be re-established. Available pharmacologic treatments offer only temporary improvement of the symptoms with varying effectiveness among individuals, making it a challenge for a physician to individualize treatment and adjust it necessarily throughout the course of the disease. Long-term treatment of PD patients with levodopa eventually leads to the appearance of motor complications, which result from both the severity of the loss of nigrostriatal dopaminergic neurons and the pulsatile administration of the drug.[8]

The motor manifestations of PD result from reduced dopaminergic inputs to the striatum. This leads to enhanced corticostriate glutamatergic drive and overactivity of the indirect pathway, resulting in hypoactivity of the globus pallidus externa. As a consequence, there is disinhibition of the subthalamic nucleus and increased excitatory drive to the globus pallidus interna and substantia nigra. The final result is excessive inhibition of the motor thalamus and brainstem locomotor regions and abnormal synchronization of oscillatory activity in the basal ganglia circuits.

METHODS

Eligibility Criteria

Studies deemed eligible were the clinical trials whose study population includes patients with PD. All of the studies are in the English language. The studies must compare patients who received Cannabinoids, in addition to the usual or accepted level of care, versus controls who received the usual or accepted level of care for Parkinson's Disease. The UPDRS score pre- and post-treatment must be documented in each study.

Exclusion Criteria

The studies excluded in the analysis are studies that did not use UPDRS as an outcome measure, studies that used animal models, and studies aside from clinical trials.

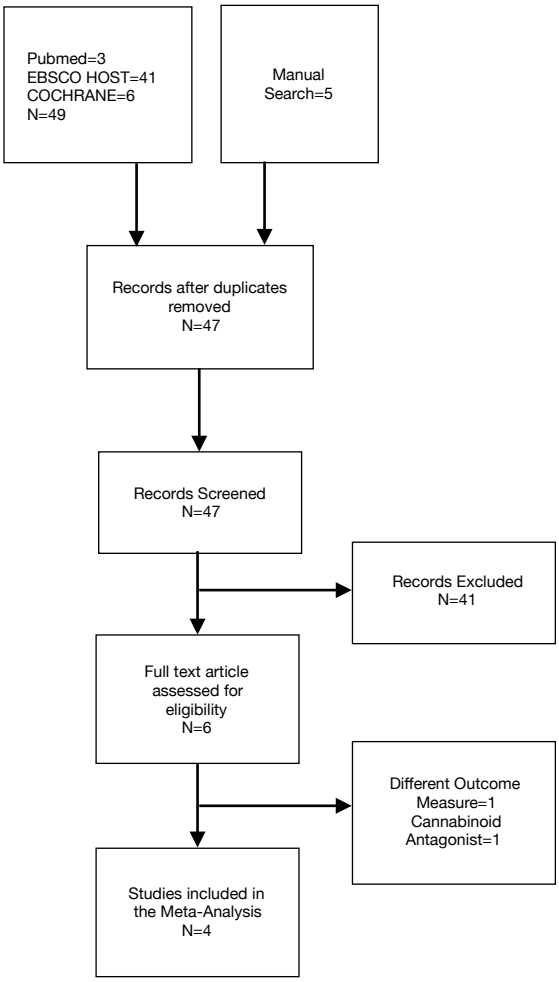
Information sources

The following databases were used to search for relevant publications dated 1990 up to October 10, 2017. PubMed via National Center for biotechnology Information, CINAHL, Medline, Academic Search, Biomedical Reference collection, via EBSCOhost, and Cochrane Library. Queries were sent to local institutions for unpublished studies compatible with the criteria for study eligibility. References were searched from citations in prior publications and reviews on the subject of study.

SEARCH STRATEGIES

Search terms that were used included (((cannabis OR cannabidiol OR marijuana OR tetrahydrocannabinol[MeSH Terms])) AND (treatment[MeSH Subheading] OR therapy[MeSH Subheading])) AND (parkinson's OR parkinsons[MeSH Terms]). (Cannabis OR Cannabidiol OR Tetrahydrocannabinol) AND UPDRS. A manual search of the reference lists of retrieved articles was also done.

Figure 1. Flowchart of Articles Selection



Study Selection

Data collection process

Data from included studies were extracted using a standardized data extraction form. Extracted data included identifying information for each study, such as author, publisher, and year published, as well as the relevant outcome in the form of UPDRS pre- and post-treatment. Baseline characteristics of treatment groups were extracted if available.

Risk of Bias (quality) assessment

Studies included for qualitative analysis were independently reviewed by three authors for compatibility with eligibility criteria, and for methodological quality in accordance to recommendations outlined in the Cochrane Handbook for Systematic Reviews.

Adherence to each criterion were scored as 'yes' (y), 'no' (n), 'unclear' (?), or 'not applicable' (n/a). Items with "n/a" were excluded from calculation for quality assessment. Based on the percentage of risk of poor methodology and/or bias, each study was assigned to the following categories: good description (80—100%), poor description (50—79%), or very poor description (0—49%).

Any conflict in the appraisal of a criterion between representative authors was settled by discussion. Studies of adequate methodological quality were subsequently included in the meta-analysis.

OUTCOME MEASURES

The primary outcome measure examined in the analysis is the UPDRS before and after treatment with cannabinoids.

Study Selection

A literature search based on databases and a manual reference search revealed 47 potentially relevant articles. Studies were chosen based on: (1) randomized or non-randomized trials, (2) The intervention therapy utilized the use of *Cannabis* or Cannabinoids in through oral consumption or smoking. 41 articles were excluded in the screening, leaving 6 articles screened for eligibility. From the 6 articles, 4 studies met the eligibility criteria, and thus were included in the meta-analysis.

Study Characteristics

Risk of Bias within studies

Methodological quality was good for the controlled trials included in the analysis, with no conspicuous anomalies in methodological quality observed. It was noted, however, that there was a disparity in follow-up times at one week and four weeks, respectively. One study also utilized a crossover design, while others randomly matched individuals to treatment groups.[12] The methodological quality of the two open label studies included was deemed to be fair to poor, as may be expected due to the nature of treatment delivery used. Smoking of *Cannabis* precludes blinding of the patient with regards to choice of treatment, thus, these studies falter in this category.[13,14] Notably, one of the two studies was unable to implement blinding of outcome assessment, raising the risk for reporting bias for this study.[13]

Synthesis of the Results

Data analysis was conducted in Review Manager 5.3 using the generic inverse variance method with mean difference as effect measure.

Table 1. Study characteristics

Author	Study Design	Sample Size	Intervention	Outcome
Chagas et. al (2014)	Randomized, double-blind, placebo-controlled study.	Control=7 Cannabidiol 75mg/day=7 Cannabidiol 300mg/day=7	Cannabidiol 75mg/day or 300mg/day for 6 weeks.	UPDRS Total UPDRS Total Motor Parkinson's Disease Questionnaire-39 UKU Side effect rating scale Assessment done after 6 weeks.
Carroll et. al (2004)	Randomized, double blind, crossover study	17 PD patients were randomized to receive oral *Cannabis* extract followed by placebo or vice versa.	*Cannabis* extract (2.5 mg of ^{9}-THC and 1.25 mg of cannabidiol per capsule) or Placebo Each treatment phase lasted for 4 weeks with an intervening 2-week washout phase.	UPDRS (32-34) dyskinesia Scale UPDRS Total UPDRS Total Motor Rush Scale Bain Scale Tablet Arm Drawing Task Assessment done after 4 weeks.
Lotan et. al (2014)	Open-Label Observational Study	22 patients	Smoking 1 dose of *Cannabis* (0.5g)	UPDRS 20-29 UPDRS Total motor Assessment done after 30minutes
Shohet et. al (2016)	Open-Label Observational Study	20 patients	Smoking 1 dose of *Cannabis* (1g)	UPDRS Total Motor Visual Analog Scale Present pain intensity scale Short form McGill Pain Questionnaire Medical Cannabis Survey National Drug and Alcohol Research Center Questionnaire Assessment Done after 30 minutes

Figure 2. Forest Plot of Comparison: Total UPDRS (fixed-effects model)

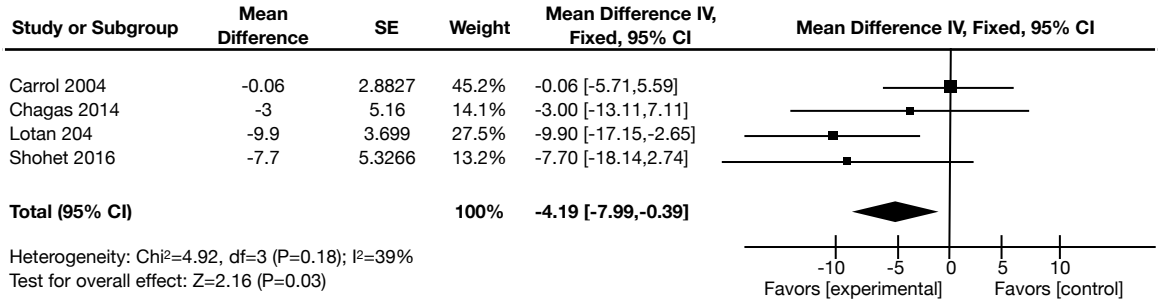
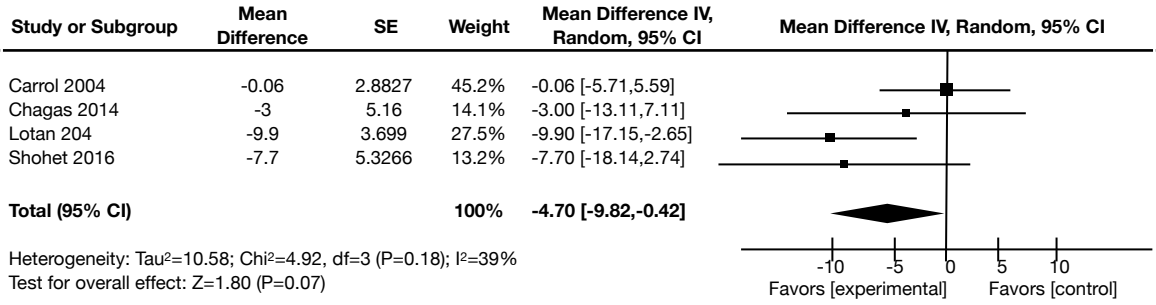


Figure 3. Forest Plot of Comparison: Total UPDRS (random-effects model)



Using the fixed effects model, the estimate of mean difference showed a significant decrease In UPDRS score. -4.19 [-7.99, -0.39] (P=0.03). Analysis using a random effects model did not result in a change in the direction of the treatment effect, however the observed treatment effect was not seen to be significant -4.70 [-9.82, 0.42] (P=0.07). In light of the similarity of fixed and random effects estimates, it may be presumed that the magnitude and direction of treatment effect is not considerably affected by study size.

Heterogeneity was not seen to be significant in both fixed- effects [Chi^2 = 4.92, df = 3 (P = 0.18); I^2 = 39%;] and random-effects analyses [Tau^2 = 10.58; Chi^2 = 4.92, df = 3 (P = 0.18); I^2 = 39%].

DISCUSSION

Alleviating symptoms of PD is truly a big challenge for a physician. Effective long-term treatment that benefit patients continue to elude us. Novel therapeutics such as *Cannabis* seem promising, but its current label as a prohibited drug in several countries has prevented it from being used for medicinal or research purposes, slowing down the progress of gathering data that may serve as groundwork for larger scale studies.

After a thorough review of the four studies, there seems to be a beneficial effect of *Cannabis* and its derivatives on the UPDRS score. A decrease was seen in the mean UPDRS using the fixed effects model, although it showed no statistical significance in the random effects model. This may be of use as a springboard for future studies of medical *Cannabis* for movement disorders.

Currently as of writing, the use of medical marijuana has been approved in the lower house of the Philippines as House Bill 180, but is still being reviewed by the Senate of the Philippines, after which must be approved by the President of the Philippines. [15] Hence, the use of medical *Cannabis* in the Philippines may be soon be seen in the horizon.

RECOMMENDATIONS

It is recommended that large-scale studies be done to increase validity of the outcome measure. Standardizing the measure of cannabinoid levels in the serum should be developed in future studies to assure that the effects of the cannabinoid result from the same amount regardless of route given (through smoking or per orem) or strain used. We expect a rise in the studies with larger samples and studies with better designs as *Cannabis* gains more credibility for its medicinal purposes among researchers, physicians, and the common public.

LIMITATIONS

The limitations of this study are: the small sample size of the studies analyzed, the time frame to which measurements were taken (short-term vs long-term), legality of the substance, and different types of vehicles and doses utilized for the administration of *Cannabis*.

FUNDING

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