A Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders

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The discovery of endocannabinoid’s role within the central nervous system and its potential therapeutic benefits have brought forth rising interest in the use of cannabis for medical purposes. The present review aimed to synthesize and evaluate the available evidences on the efficacy of cannabis and its derivatives for psychiatric, neurodegenerative and movement disorders. A systematic search of randomized controlled trials of cannabis and its derivatives were conducted via databases (PubMed, Embase and the Cochrane Central Register of Controlled Trials). A total of 24 reports that evaluated the use of medical cannabis for Alzheimer’s disease, anorexia nervosa, anxiety, dementia, dystonia, Huntington’s disease, Parkinson’s disease, post-traumatic stress disorder (PTSD), psychosis and Tourette syndrome were included in this review. Trial quality was assessed with the Cochrane risk of bias tool. There is a lack of evidence on the therapeutic effects of cannabinoids for amyotrophic lateral sclerosis and dystonia. Although trials with positive findings were identified for anorexia nervosa, anxiety, PTSD, psychotic symptoms, agitation in Alzheimer’s disease and dementia, Huntington’s disease, and Tourette syndrome, and dyskinesia in Parkinson’s disease, definitive conclusion on its efficacy could not be drawn. Evaluation of these low–quality trials, as rated on the Cochrane risk of bias tools, was challenged by methodological issues such as inadequate description of allocation concealment, blinding and underpowered sample size, More adequately powered controlled trials that examine the long and short term efficacy, safety and tolerability of cannabis for medical use, and the mechanisms underpinning the therapeutic potential are warranted.

KEY WORDS: Cannabis; Cannabinoids; Randomized controlled trial; Mental disorders; Movement disorders; Neurodegenerative diseases.

INTRODUCTION

Cannabis (marijuana) has long been used for medical and recreational purposes. The Cannabis sativa and Cannabis indica are two common species used for consumption. Between the two species, C. sativa has comparatively higher delta-9-tetrahydrocannabinol (THC) concentration while C. indica has comparatively higher cannabidiol concentration. Cannabinoids can be classified into three subtypes, endocannabinoids (naturally present in human body), phytocannabinoids (present in cannabis plant) and synthetic cannabinoids (produced chemically). Presently, over 60 different types of pharmacologically active cannabinoids have been identified and isolated from the cannabis plant.1) These include the exogenous cannabinoids such as the psychoactive THC and non-psychoactive cannabidiol, as well as the endogenous cannabinoids such as anandamide, which affects most systems in the human body, especially the central nervous system. The cannabinoid binds to two types of G protein-coupled receptors: CB₁, which are most abundant in the brain, and CB₂, which are expressed on cells in the immune system where inflammation is modulated.1) Hence, cannabinoids are involved in psychomotor coordination, memory, mood, and pain.2) Given the expression of these receptors in the human body, and the interactions between cannabinoids with neurotransmitters and neuromodulators, such as dopamine, glutamate, serotonin, gamma-amino-butyric acid (GABA), it has been thought that cannabis may potentially confer some degree of medical benefit.

Medical cannabis refers to the use of cannabis and its derivatives to treat disease and relieve symptoms.3) Common commercially available cannabinoids for medical use are presented in Table 1.4-6) Testing of other synthetic cannabinoid compounds such as Epidiolex (GW
Table 1. Summary of cannabinoids

| Generic name | Trade name | Administration method | Formulation | Dosage | Pharmacokinetics |
|--------------|------------|-----------------------|-------------|--------|-----------------|
| Dronabinol   | Marinol    | Oral capsule          | Synthetic THC | 2.5 mg, 5 mg, 10 mg | \(t_{\text{max}}=2-4 \text{ hr}\). Completely absorbed (90-95%) after a single dose. Alpha (plasma) half-life: 4 hr. Beta (tissue) half-life: 25-36 hr* |
| Nabilone     | Cesamet    | Oral capsule          | Synthetic structural analogue of THC | 1 mg | \(t_{\text{max}}=2 \text{ hr}\). Alpha (plasma) half-life: 2 hr. Beta (tissue) half-life: 35 hr* |
| Nabiximols   | Sativex    | Oromucosal spray      | Whole plant cannabis extract | 2.7 mg THC and 2.5 mg CBD, per spray (100 \(\mu\)l) | \(t_{\text{max}}=98-253 \text{ min}\). Variable plasma half-life of 85-130 min. Clearance within 12-24 hr after dose* |
| CBD THC      | None Namisol | Oral capsule          | Cannabis plant extract | Variable | \(t_{\text{max}}=1-2 \text{ hr}\). No available information in humans.|

THC, tetrahydrocannabinol; CBD, cannabidiol.

*Marinol (Abbott Products, 2010), Cesamet (Valeant Canada, 2009), and Sativex (GW Pharmaceutical, 2010).

Pharmaceuticals, Cambridge, UK), Namisol (Echo Pharmaceuticals, Weesp, the Netherlands) and Cannador (Society for Clinical Research, Berlin, Germany) are currently underway. These cannabinoid formulations of varying THC or cannabidiol concentration and/or ratio have been widely studied for a variety of illnesses, most notably somatic conditions like pain and spasticity. More recently, there has been a growing interest in the neuroprotective potential of cannabinoids for neurological conditions, and the antipsychotic properties of cannabidiol. Preclinical evidences suggest that cannabinoids may attenuate neurodegeneration by reducing excitotoxicity and oxidative damage via CB1 and CB2 receptors and receptor-independent mechanisms. In the case of cannabidiol, there are indications that cannabidiol modulates the endocannabinoids system by enhancing anandamide levels, thereby reducing psychotic symptoms. Although reviews of preclinical and clinical studies have been conducted on movement disorders and psychosis, the aim of the present review is to provide a more in-depth evaluation of the efficacy of medical cannabinoids by appraising the quality of evidences from clinical studies across a broader range of neurodegenerative disorders and psychiatric conditions.

METHODS

Types of Studies

Randomized controlled trials that compared and examined the pharmacological intervention of cannabis (in any preparation form, and any route of administration) with placebo or other active treatments were included. Other quantitative study designs such as cohort studies, retrospective chart review studies, and case studies were excluded. Opinion and discussion papers were also excluded. This review only considered studies on human participants that were published in English-language.

Types of Participants

People of any age and sex with any of the following conditions, and/or clinically diagnosed with movement disorders (e.g., dystonia, Huntington’s disease, Parkinson’s disease, Tourette syndrome), neurological conditions (e.g., Alzheimer’s disease, dementia, amyotrophic lateral sclerosis [ALS]) and psychiatric condition (e.g., psychosis, schizophrenia, anxiety).

Types of Interventions

Any form of cannabis for medical use irrespective of the route of administration, duration of intervention or dosage: Smoked cannabis, natural or synthetic cannabinoid including, THC, cannabino (CBN), cannabidiol, or combinations of abovementioned agents. The comparators included placebo, usual care, other types of active treatments, or derivatives of cannabis.

Search Strategy

An electronic search of human studies published in English-language was conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials.
(CENTRAL) from its inception to present (April 2017), using the following keywords: “randomized controlled trial (RCT), cannabinoids, cannabis, tetrahydrocannabinol, THC, cannabidiol, movement disorder, neurodegenerative, psychiatric, dystonia, Huntington’s disease, Parkinson’s disease, Tourette syndrome, Alzheimer’s disease, dementia, ALS, psychosis, schizophrenia, anxiety”. The reference lists of retrieved papers were also reviewed for additional papers. The full texts retrieved were assessed for relevance based on the objectives and inclusion criteria of this review. Studies in which full text were unavailable were excluded.

### Data Extraction and Quality Assessment

The data extracted from each report included the study type, sample characteristics, type and dosage of intervention, primary outcome measures, side effect and adverse events. Studies were evaluated for methodological quality using the Cochrane risk of bias tool,[12] on sequence generation, allocation concealment, blinding, incomplete data and selective outcome reporting. The ratings were high, low or unclear risk of bias (Table 2).[13-36] The assessment of methodological quality was performed by two independent raters. Discrepancies were resolved by mutual discussion.

### Table 2. Cochrane risk of bias tool ratings of included studies

| Study                                      | Psychiatric condition | Neurodegenerative disorders | Movement disorders |
|--------------------------------------------|-----------------------|------------------------------|--------------------|
|                                            |                       |                              |                    |
|                                            | Anorexia Nervosa      |                              |                    |
| Gross et al. (1983)                        | ?                     | ?                            |                    |
| Andries et al. (2014)                      | +                     | +                            |                    |
|                                            | Anxiety               |                              |                    |
| Fabbre et al. (1981)                       | ?                     | –                            | –                  |
| Glass et al. (1981)                        | ?                     | ?                            | –                  |
| Zuardi et al. (1982)                       | ?                     | ?                            | ?                  |
| Bergamaschi et al. (2011)                  | ?                     | ?                            | ?                  |
| Crippa et al. (2011)                       | ?                     | ?                            | ?                  |
| Post-traumatic stress disorder             | Jetty et al. (2015)   | ?                            | ?                  |
|                                            | Psychotic symptoms    | ?                            | –                  |
| Leweke et al. (2012)                       | +                     | ?                            | –                  |
|                                            | Alzheimer’s disease   |                              |                    |
| Volcier et al. (1997)                      | ?                     | ?                            | ?                  |
|                                            | Dementia              |                              |                    |
| Walther et al. (2011)                      | ?                     | ?                            | ?                  |
| van den Elsen et al. (2015)                | +                     | ?                            | ?                  |
| van den Elsen et al. (2015)                | +                     | ?                            | ?                  |
|                                            | Amyotrophic lateral sclerosis |                |                    |
| Weber et al. (2010)                        | +                     | ?                            | ?                  |
|                                            | Movement disorders    |                              |                    |
|                                            | Dystonia              |                              |                    |
| Fox et al. (2002)                          | +                     | +                            | ?                  |
| Zadikoff et al. (2011)                     | +                     | ?                            | ?                  |
|                                            | Huntington's disease  |                              |                    |
| Consroe et al. (1991)                      | ?                     | ?                            | ?                  |
| Curtis et al. (2009)                       | ?                     | +                            | ?                  |
| López-Sendón Moreno et al. (2016)          | +                     | ?                            | ?                  |
|                                            | Parkinson’s disease   |                              |                    |
| Sieradzan et al. (2001)                    | ?                     | ?                            | ?                  |
| Carroll et al. (2004)                      | +                     | ?                            | ?                  |
| Chagas et al. (2014)                       | ?                     | ?                            | ?                  |
|                                            | Tourette syndrome     |                              |                    |
| Müller-Vahl et al. (2002)                  | ?                     | ?                            | ?                  |
| Müller-Vahl et al. (2003)                  | ?                     | ?                            | ?                  |

*+, low risk of bias; –, high risk of bias; ?, unclear risk of bias.
RESULTS

The search yielded 931 records (hits), of which 916 records remained after removing duplicates. Eighty-six records were then considered as potentially relevant after evaluation of title and abstract. The reference lists of these records were also reviewed. The full texts of these records were retrieved and reviewed based on the inclusion criteria and objectives of this review. A total of 62 records were excluded and 24 records were included in this review (Fig. 1). Of the 24 reports (480 participants), 18 were crossover trials, 6 were parallel trials. All of the studies were conducted in Western societies.

Psychiatric Disorders

Anorexia nervosa

Two studies (36 participants), rated as having a low and high risk of bias, evaluated cannabinoids for the treatment of anorexia nervosa. In an early crossover trial involving 11 females with anorexia nervosa, titrated THC 7.5 mg (2.5 mg, three times a day) to a maximum of 30 mg (10 mg, three times a day) showed similar weight gain to titrated diazepam 3.0 mg (1 mg, three times a day) to 15.0 mg (5 mg, three times a day). Three patients in the THC treated group were withdrawn due to severe dysphoric reactions. More recently, in two 4-week treatments separated by a 4-week washout period, dronabinol (2.5 mg, twice a day) produced significant weight gain of 0.73 kg ($p < 0.01$), compared to placebo.
| Study               | Design/duration | Condition                          | Sample characteristics* | Intervention (No. of patients) | Outcome | Side effects / adverse events | Results                                      | Cochrane risk of bias |
|--------------------|-----------------|------------------------------------|-------------------------|---------------------------------|---------|-----------------------------|---------------------------------------------|----------------------|
| Gross et al. (1983) | Double blind Crossover | Anorexia nervosa                  | n=11; All females; Mean age, 23.6 yr | THC 2.5-10 mg·3; Diazepam 1.5 mg·3 | Primary: Weight gain | 3 withdrawn due to severe dysphoria | No significant difference between groups on weight gain | High                 |
| Andries et al. (2014) | Double blind Crossover | Anorexia nervosa                  | n=25; All females | Dronabinol 2.5 mg·2; Placebo | Primary: Weight gain Secondary: EDI-2 | No severe adverse event | Significant weight gain of 0.73 kg with dronabinol (<0.01) | Low                  |
| Anxiety            |                 |                                    |                         |                                 |         |                             |                                             |                     |
| Fabre et al. (1981) | Double blind Parallel (28 days) | Anxiety                  | n=20; 15:5; 9:41 yr (mean age, 29 yr) | Nabilone 1 mg·3; Placebo | Hamilton rating scale for anxiety | Dry mouth; Dry eyes; Drowsiness | Improvement in anxiety in nabilone group compared to placebo group (<0.0001) | High                 |
| Glass et al. (1981) | Single blind Crossover | Generalized anxiety disorder      | n=8; 3:5; 22:30 yr | Nabilone 2 mg; Placebo | Heart rate, blood pressure; POMS; Anxiety-interviews and spontaneous reports | Light-headedness; Headache; Nausea; Sleepiness | Lack of antianxiety effects | High                 |
| Zuardi et al. (1982) | Double blind Crossover | Anxiety induced by THC in healthy volunteers | n=8; 6:2; 20:38 yr; Mean age, 27 yr | THC 0.5 mg·kg; CBD 1 mg·kg; Mixture (THC 0.5 mg·kg+CBD 1 mg·kg); Diazepam 10 mg; Placebo | VAMS | No information | CBD attenuated but did not completely block the anxiety induced by THC | Unclear               |
| Bergamaschi et al. (2011) | Double blind Parallel | Anxiety induced by simulated public speaking in social phobia patients | n=36 (24, generalized social anxiety disorder; 12, healthy controls); 18:18; Mean age, 22.9-24.6 yr | CBD 600 mg; Placebo | VAMS; SSPS-N; Physiological measures (blood pressure, heart rate, and skin conductance) | No information | BD treatment significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech; placebo group scored higher on these measures compared to healthy controls | High                 |
| Crippa et al. (2011) | Double blind Crossover | Generalized social anxiety disorder | n=10; 1:9 males; 20-33 yr (mean, 24.2 yr) | CBD 400 mg; Placebo | VAMS; Regional cerebral blood flow using SPECT technique | No information | Significant decrease in subjective anxiety (<0.001); Reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus (<0.001, uncorrected), and increased ECD uptake in the right posterior cingulate gyrus (<0.001, uncorrected) | Unclear               |
Anxiety

The anti-anxiety efficacy of cannabinoids was assessed in 5 studies. In 38 patients and 44 healthy volunteers (Table 3). Three studies were rated as high risk of bias and 2 as unclear risk of bias. Two early studies indicated equivocal anti-anxiety effects of nabilone. In a double-blind study involving 20 patients, compared to placebo, 1 mg nabilone administered twice daily for 28 days significantly improved anxiety measured by the Hamilton Rating Scale for Anxiety. However, this was not observed in another crossover trial involving 8 symptomatic volunteers. In another study involving 24 generalized social anxiety disorder patients, a single dose of 600 mg cannabidiol was associated with a significant decrease in subjective anxiety measured by the visual analogue mood scale (p < 0.001). In a parallel study, 10 male patients with generalized social anxiety disorder were randomly assigned to receive either a single dose of 400 mg cannabidiol or placebo. Pre-treatment of cannabidiol significantly reduced anxiety measured by the visual analogue mood scale compared to placebo (p < 0.001). Specifically, in a double-blind study involving 20 patients, compared to placebo, 1 mg nabilone administered twice daily for 28 days significantly improved anxiety measured by the Hamilton Rating Scale. In another study involving 8 healthy volunteers with a history of cannabis use, cannabidiol attenuated anxiety induced by THC. More recently, in a parallel study, 10 male patients with generalized social anxiety disorder were randomly assigned to receive either a single dose of 600 mg cannabidiol or placebo. Pre-treatment of cannabidiol significantly reduced anxiety measured by the visual analogue mood scale compared to placebo (p < 0.001).

Table 3.

| Study | Design/ duration | Condition | Sample characteristics* | Intervention (No. of patients) | Outcome | Side effects / adverse events | Results | Cochrane risk of bias |
|-------|------------------|-----------|-------------------------|--------------------------------|---------|-----------------------------|---------|----------------------|
| Jetly et al. (2013) | Double blind Crossover | PTSD associated nightmares | n=10 | Nabilone 0-5-3.0 mg | CAPS | Dry mouth | Significant improvement in: | Unclear |
| | | | All males | Placebo | CGI-C | CAPS recurring and Distressing Dream scores (p=0.03) | |
| | | | Mean age, 43.6 yr | PSQ dream rating scale | | HEADACHE | | |
| | | | | WBQ | | | |
| Post-traumatic stress disorder (PTSD) | | | | | | | |
| | | | | | | | |

Psychotic symptoms

Leweke et al. (2012) | Double blind Parallel | Schizophrenia patients | n=42 | CBD 800 mg/day | PANSS | No information | Decreased BPRS and PANSS scores with no difference between both treatment groups | High |
| | | | Mean age, 29.7 yr | Amiliperide 800 mg/day | BPRS | | | | |
| | | | | | | | | | |

THC, tetrahydrocannabinol; EDI-2, Eating Disorder Inventory-2; POMS, Profile of Mood States; CBD, cannabidiol; STAI, State-Trait Anxiety Inventory; ARCI-Ma, Addiction Research Center Inventory for marijuana effects; VAMS, visual analogue mood scale; BPRS-N, Negative Self-statement scale; SPECT, single-photon emission computed tomography; ECD, ethylene cysteine dimer; CAPS, Clinicians Administered PTSD scale; CGI-C, Clinical Global Impression of change; WBQ, General Well-Being Questionnaire; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale.

*Total (completed)/male:female/age.
| Study                  | Design/duration | Condition                          | Sample characteristics | Intervention (No. of patients) | Outcome | Side effects/adverse events | Results                                                                 | Cochrane risk of bias |
|------------------------|-----------------|------------------------------------|------------------------|-------------------------------|---------|----------------------------|--------------------------------------------------------------------------|-----------------------|
| Alzheimer’s disease    | Double-blind Crossover | Disturbed behavior in Alzheimer’s disease | n=12 11:1 65-82 yr Mean age 72.7 yr | Dronabinol 2.5 mg Placebo | CMAI Lawton observed affect scale | Common side effects: Anxiety Emotional lability Tiredness Somnolence | Decreased severity of disturbed behavior (CMAI, p=0.05) Decreased negative affect (p=0.045), but not positive affect | Unclear               |
| Dementia               | Crossover       | Nighttime agitation in Alzheimer’s disease | n=2                      | Dronabinol 2.5 mg Placebo | Nonparametric circadian rhythm analysis | No adverse event | Reduced nighttime agitation and strengthened circadian rhythms | Unclear               |
| van den Elsen et al.   | Double-blind Crossover | Dementia                          | n=54 Mean age 76.4 yr | THC (Namisol) 1.5 mg-3 Placebo | NPI CMAI Barthel index QoL-AD CCGIC | Common side effects: Dizziness Somnolence | No significant difference on all measures | Unclear               |
| van den Elsen et al.   | Double-blind Crossover | Dementia                          | n=22 Mean age 76.4 yr | THC (Namisol) 0.75-1.5 mg-2 Placebo | NPI CMAI ZBI | Lack of information on common adverse event | No significant difference on all measures | Unclear               |
| Amyotrophic lateral sclerosis (ALS) | Double-blind Crossover | ALS                              | n=27 20:7 34-48 yr (mean 57 yr) | THC 5 mg-2 Placebo | Primary: Daily cramp severity (VAS) Secondary: ALSFRS-R ALSAQ-40 SDQ24 | 2 serious adverse events | No significant difference on all measures | Unclear               |

CMAI, Cohen-Mansfield Agitation Inventory; NPI, Neuropsychiatric Inventory; THC, tetrahydrocannabinol; QoL-AD, Quality of Life in Alzheimer’s Disease scale; CCGIC, Caregiver Clinical Global Impression of Change; ZBI, Zarit Burden Interview; VAS, visual analogue scale; ALSFRS-R, ALS functional rating scale revised; ALSAQ-40, ALS assessment questionnaire; SDQ24, Sleep Disorder Questionnaire.

*• Total (completed)/• male:female/¥ age.
treatments as indexed by the Brief Psychiatric Rating Scale and the Positive and Negative Syndrome Scale, no statistical significant difference was reported between groups. However, cannabidiol treatment displayed a superior side-effect profile, compared to amisulpride treatment. Specifically, cannabidiol was associated with significantly smaller weight gain, lower prolactin levels and lesser extrapyramidal symptoms.

Neurodegenerative Disorders

Alzheimer’s disease

One trial on Alzheimer’s disease, rated as unclear risk of bias, examined the use of dronabinol for managing Alzheimer’s disease (Table 4). In a 6-week crossover trial, 2.5 mg dronabinol appeared to reduce disturbed behaviors in 12 patients, as measured by the Cohen-Mansfield Agitation Inventory \( (p=0.05) \). Two recent trials on showed that THC capsules (0.75-1.5 mg) did not improve neuropsychiatric symptoms in patients with dementia.

Dementia

Three trials on dementia (78 participants), rated as having an unclear risk of bias, showed equivocal results. In a 4-week trial, 2.5 mg dronabinol reduced night-time agitation and strengthened circadian rhythms in the 2 patient enrolled in the study. However, two recent trials on showed that THC capsules (0.75-1.5 mg) did not improve neuropsychiatric symptoms in patients with dementia.

Amyotrophic lateral sclerosis

The only RCT was conducted in 27 patients with ALS. In this crossover trial, patients were randomized to receive 2 weeks of 5 mg THC twice daily or placebo, separated by a 2-week washout period. There is a lack of treatment effect on cramp intensity and number of cramps. This study was rated as having an unclear risk of bias.

Movement Disorders

Dystonia

Two trials (24 participants) indicated lack of evidence on the use of cannabinoid for dystonia (Table 5). The studies were rated as having an unclear risk of bias and high risk of bias. In a crossover trial, 15 patients with primary dystonia received a single dose of 0.03 mg/kg nabiboline or placebo. Although four patients reported a subjective improvement in dystonia severity, there was no significant difference between groups on the primary endpoint at 60, 120 or 180 minutes post-treatment, as indexed by the Burke-Fahn-Marsden dystonia scale. In another 8-week crossover trial, 9 female patients with cervical dystonia were randomized to receive titrated 2.5 mg dronabinol, up to 3 tabs twice a daily (15 mg/day) or placebo. There was no significant treatment effect of dronabinol on cervical dystonia as indexed by the Toronto Western Hospital Spasmodic Torticollis Rating Scale, or any of the secondary measures.

Huntington’s disease

The efficacy of cannabinoids for Huntington’s disease was assessed in 3 trials (84 participants). All studies were rated as having an unclear risk of bias. A 6-week crossover trial evaluated cannabidiol (a total of 10 mg/kg over two doses daily) for chorea in 15 patients with Huntington’s disease. There was no significant difference between placebo and cannabidiol on chorea severity measured by the Marsden and Quinn’s Chorea Severity Scale. Conversely, in another 10-week placebo-controlled crossover trial, nabiboline (1 or 2 mg) showed significant treatment effect as measured by the total motor and chorea score on the Unified Huntington’s Disease Rating Scale (UHDRS). More recently, no significant treatment effect was reported on the UHDRS, in a sample of 25 patients who receive nabiximols (up to 12 sprays/day) in a crossover trial.

Parkinson’s disease

Three studies (49 participants) examined the use of cannabinoids for Parkinson’s disease. All studies were rated as having an unclear risk of bias. In an early crossover trial involving 9 Parkinson’s disease patients with dyskinesia, 0.03 mg/kg nabiboline significantly improved dyskinesia as indexed by the Rush dyskinesia disability scale. Conversely, in a 4-week dose escalation crossover trial, 19 Parkinson’s disease patients with levodopa-induced dyskinesia were administered with titrated canna- dor up to 0.25 mg/kg THC or placebo. Cannador failed to show any significant treatment effect on the primary outcome, the Unified Parkinson’s Disease Rating Scale (UPDRS) dyskinesia items, as well as the secondary measures such as motor symptoms and quality of life (39-item Parkinson’s disease questionnaire, PDQ-39). More recently, in a placebo-controlled trial, 21 patients with Parkinson’s disease were randomized to receive cannabidiol (75 mg/day or 300 mg/day) or placebo for 6 weeks. There was no statistical significant difference between the groups on the UPDRS. However, a significant improvement was reported for PDQ-39, particularly the activities of daily living and stigma subscale for the 300 mg/day cannabidiol group.
| Study                        | Design/duration | Condition                        | Sample characteristics               | Intervention (No. of patients) | Outcome                                                                 | Side effects / adverse events                                                                 | Results                                                                 | Cochrane risk of bias |
|-----------------------------|-----------------|----------------------------------|-------------------------------------|-------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------|
| Dystonia                    |                 |                                  |                                     |                               |                                                                          |                                                                                              |                                                                        |                       |
| Fox et al. (2002)           | Double-blind Crossover | Dystonia primary                  | n=15 * 6:9 * 28-63 yr (mean, 47 yr) | Nabillone 0.03 mg/kg/ Placebo | Dystonia-movement scale scores                                          | 2 patients withdrawn due to postural hypotension and marked sedation                         | No significant reduction in dystonia movement scale scores              | Unclear               |
| Zadikoff et al. (2011)      | Double-blind Crossover | Cervical dystonia                 | n=9 * All females * Mean age, 60 yr | Dronabinol up to 15 mg/day/ Placebo | TWSTRS-motor severity, daily activities, pain                           |                                                                                              | No significant difference on all subcales of TWSTRS                     | High                  |
| Huntington’s disease         |                 |                                  |                                     |                               |                                                                          |                                                                                              |                                                                        |                       |
| Consroe et al. (1991)       | Double-blind Crossover | Chorea severity in Huntington’s disease | n=15 * 8.7 * 17-66 yr (median, 52 yr) | CBD 10 mg/kg/ Placebo        | Marsden and Quinn’s Chorea Severity Scale                               | No information                                                                                   | No significant difference on chorea severity                            | Unclear               |
| Curtis et al. (2009)        | Double-blind Crossover | Huntington’s disease              | n=44 * 22:22 * 34-72 yr (mean, 52 yr) | Nabillone 1 or 2 mg/ Placebo | UHDRS                                                                    | Common side effects:                                                                 | Significant treatment effect of nabillone on motor and chorea subscale of UHDRS compared to placebo, but no difference between 1 and 2 mg nabillone | Unclear               |
| López-Sendón et al. (2016)  | Double-blind Crossover | Huntington’s disease              | n=25 * 14:11 * Mean age, 47.6 yr | Nabilimeols up to 12 sprays/day/ Placebo | UHDRS                                                                    | Common side effects:                                                                 | No significant difference on all measures                                | Unclear               |
| Parkinson’s disease          |                 |                                  |                                     |                               |                                                                          |                                                                                              |                                                                        |                       |
| Sierra et al. (2001)        | Double-blind Crossover | Dyskinesia in Parkinson’s disease | n=9 * 4:5 * Mean age, 67 yr        | 0.03 mg/kg nabillone/ Placebo | RDS                                                                      | Common side effects:                                                                 | Significant 22% reduction on RDS for treatment group                  | Unclear               |
| Caroli et al. (2004)        | Double-blind Crossover (4 weeks) | Dyskinesia in Parkinson’s disease | n=19 * 12:9 * Mean age, 67 yr | 2.5 mg THC:1.25 mg CBD-cannador/ Placebo | UPDRS                                                                   |                                                                                              | Lack of treatment effect of THC:CBD for dyskinesia assessed by UPDRS      | Unclear               |
| Chagas et al. (2014)        | Double-blind Parallel (6 weeks) | Parkinson’s disease               | n=21 * 15:6 * Mean age, 67 yr | CBD 75 or 300 mg/day/ Placebo | UPDRS/ PDQ-39                                                           | No reported side effects                                                                 | No significant difference on UPDRS                                     | Unclear               |
There is a lack of evidence on the therapeutic effects of cannabinoids for ALS and dystonia. Although results were inconsistent, there appears to be some low-quality evidence of cannabinoids for anorexia nervosa, anxiety, PTSD, psychotic symptoms, agitation in Alzheimer’s disease and dementia, Huntington’s disease, and Tourette syndrome, and dyskinesia in Parkinson’s disease. However, concrete conclusions about its efficacy could not be made due to the unclear risk of bias presented by these trials, as rated on the Cochrane risk of bias tool. Methodological issues such as inadequate description of allocation concealment and blinding, varying cannabinoid formulations and doses, and small sample sizes limit its potential clinical utility.

Consistent with previous case studies and clinical trials, the only RCT on cannabis and Tourette syndrome, and dykeinesia in Parkinson’s disease reported a significant improvement of tics on the Tourette Syndrome-Clinical Global Impressions Scale for THC, but not placebo. Similarly, THC significantly reduced tic severity compared to placebo.

**DISCUSSION**

**Table 5.**

| Study | Design/duration | Condition | Sample characteristics | Intervention (No. of patients) | Outcome | Side effects / adverse events | Results | Cochrane risk of bias |
|-------|-----------------|-----------|------------------------|------------------------------|---------|------------------------------|---------|----------------------|
| Müller-Vahl et al. (2002) | Double-blind Crossover | Tic in Tourette syndrome | n=12 | Delta-9-THC 5-10 mg | TSSL | Common side effects: Tiredness, Dizziness | Significant improvement of tic. (p=0.015) | Unclear |
| Müller-Vahl et al. (2003) | Double-blind Parallel | Tourette syndrome | n=24 | THC up to 10 mg | TS-CGI | Common side effects: Tiredness, Dizziness, Dry mouth | Significant improvement in TS-CGI, STSSS, YGTSS, TSSL | High |

**TWSTRS, Toronto Western Hospital Spasmodic Torticollis Rating Scale; CBD, cannabidiol; UHDRS, Unified Huntington’s Disease Rating Scale; RDS, Rush dykeinesia disability scale; THC, tetrahydrocannabinol; UPDRS, Unified Parkinson’s Disease Rating Scale; POQ-39, 39-item Parkinson’s disease questionnaire; TSSL, Tourette Syndrome Symptoms List; STSSS, Shapiro Tourette syndrome severity scale; YGTSS, Yale Global Tic Severity Scale; TS-CGI, Tourette Syndrome-Clinical Global Impression Scale.**

*Total (completed)/male:female/age.*
fect of varying doses, and long term safety and efficacy are needed to supplement current findings.

For trials involving movement and neurodegenerative disorder, the limited number of trials, lack of quantitative data and underpowered samples inhibits reliable conclusion from being made. Nonetheless, the expression of endocannabinoid receptors (CB1 and CB2) in the basal ganglia and the immune systems could indicate the protective role of cannabinoids for movement and neurodegenerative disorder. This warrants future studies, in vivo and animal models, to clarify the biological mechanisms underpinning the modulatory role of cannabinoids.

Cannabinoids appear to be well-tolerated in these trials. The common short-term effects included dry mouth, dizziness, tiredness, and headache. Indeed, reviews that discussed the adverse effect of cannabis administration have reported that cannabis or cannabinoid administration was associated with a greater risk of non-serious adverse events. This illuminates the need to conduct trials that compare the effects and efficacy of cannabinoids with existing treatment. This would provide a clear cost-benefit evaluation of medical cannabis.

Overall, there are few RCTs that evaluated the efficacy of cannabis for psychiatric, neurodegenerative and movement disorders. While inconsistency in results may be attributed to different outcome measures used, varying doses and formulations, it raises the question on the mechanism underlying the therapeutic benefits of cannabinoids across indications with different pathophysiology (i.e., psychiatric, neurodegenerative and somatic conditions). Clarification of the cellular pathways and mechanisms of cannabinoids for various indications could reveal the cascading effect of cannabinoids and its interactions with pathways associated with these indications.

CONCLUSION

While there are trials that suggest potential benefit of cannabinoids for anorexia nervosa, anxiety, PTSD, psychotic symptoms agitation in Alzheimer’s disease and dementia, Huntington’s disease, and Tourette syndrome, and dyskinesia in Parkinson’s disease, insufficient conclusion could be made due to the low quality of evidence as indexed by the Cochrane risk of bias, and underpowered samples. An improved knowledge of the precise mechanism of cannabinoids at the cellular level could provide insights on the therapeutic benefits of cannabinoids for movement, psychiatric and neurodegenerative disorder. This could facilitate development of cannabinoid formulations and the conduct of clinical trials on these indications.

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