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REVIEW

# Cannabinoids and Tremor Induced by Motor-related Disorders: Friend or Foe?

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**Abstract** Tremor arises from an involuntary, rhythmic muscle contraction/relaxation cycle and is a common disabling symptom of many motor-related diseases such as Parkinson disease, multiple sclerosis, Huntington disease, and forms of ataxia. In the wake of anecdotal, largely uncontrolled, observations claiming the amelioration of some symptoms among cannabis smokers, and the high density of cannabinoid receptors in the areas responsible for motor function, including basal ganglia and cerebellum, many researchers have pursued the question of whether cannabinoid-based compounds could be used therapeutically to alleviate tremor associated with central nervous system diseases. In this review, we focus on possible effects of cannabinoid-based medicines, in particular on Parkinsonian and multiple sclerosis-related tremors and the common probable molecular mechanisms. While, at present, inconclusive results have been obtained, future investigations should extend preclinical studies with different cannabinoids to controlled clinical trials to determine potential benefits in tremor.

**Keywords** Tremor · Cannabinoid · Parkinson's disease · Multiple sclerosis · Huntington's disease · Ataxia

Apothecaries were not worth a pin,
If Hemp seed did not bring their commings in;
Oyles, Vnguents, Sirrops, Minerals, and Baulmes,
(All Natures treasures, and th' Almighties almes,)
Emplasters, Simples, Compounds, sundry drugs
With Necromanticke names like fearefull Bugs,
Fumes, Vomits, purges, that both cures, and kils,
Extractions, conserues, preserues, potions, pils,
Ellixers, simples, compounds, distillations,
Gums in abundance, brought from foreigne nations.
John Taylor (1580–1653)

For several millennia, many civilizations have used *Cannabis sativa* for assorted purposes [1]. This magical plant was eulogized for its recreational use and its tremendous beneficial effects in painless surgeries [2, 3]. To date, >100 terpenophenolic cannabinoids have been isolated from *C. sativa*, among these, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), as the primary and main psychoactive constituent, cannabidiol (CBD), cannabinol, cannabichromene, and cannabigerol are of particular interest [4–6]. In the light of previous studies, the cannabis plant has been shown to play a role as an antiemetic, appetite stimulant, analgesic, euphoriant, anti-inflammatory agent, anticonvulsant, and as a sedative [2, 4, 7–20]. It has also been noted that cannabis can impair memory and cognition [21, 22]. However, the clinical applications of cannabis remain circumscribed, largely owing to the known psychoactive effects of $\Delta^9$-THC [23, 24]. Cannabinoids exert their pharmacological and physiological activities predominantly through G protein-coupled cannabinoid $CB_1$ and $CB_2$ receptors ($CB_1R$ and $CB_2R$, respectively) [25, 26]. Following the

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discovery of cannabinoid receptors in rat brain in 1980, the location of these receptors was mapped in mammalian species, including humans, and were shown to be ubiquitous in hippocampus, basal ganglia, and cerebellum. Some years later, in 1990 and 1993, $CB_1R$ and $CB_2R$, respectively, were cloned [27–29]. The predominant expression of these receptors, in particular $CB_1R$, and the presence of endocannabinoids in brain areas responsible for the management of movements, such as basal ganglia and cerebellum, together with the conspicuous changes in endocannabinoid transmission in the brains of individuals affected by motor disorders, provides a compelling conceptual argument that cannabinoid-based compounds may have the potential to alleviate symptoms of these diseases and provide a novel area of research [30, 31]. The aim of the current paper is to review the literature on the effects of cannabinoids in motor disorders associated with tremor, with the goal of highlighting possible therapeutic applications. Tremor is a rhythmic, unintentional, oscillatory, and twitching movement, and a clinical manifestation of numerous disorders such as multiple sclerosis (MS), Parkinson's disease (PD), and Huntington's disease (HD), which all affect central areas associated with motor control [32–34]. Tremor has been categorized, based on its etiology, origin, and clinical presentations, into 6 main groups [35]. Despite significant efforts to find an effective pharmacological intervention, as yet there is limited availability of efficient treatments to reduce tremor markedly [36]. However, new insights into the molecular basis of diseases associated with tremor might lead to such a discovery. As argued below, cannabinoids could represent a promising avenue of future research.

## Cannabinoid Receptors and Signaling in relations to Central Nervous System Dysfunction Associated with Tremor

Endocannabinoids are produced "on demand" and act as a retrograde messenger on presynaptic cannabinoid receptors. Although additional molecular targets may be involved, cannabinoid receptors have been divided into 2 major subtypes, $CB_1R$ and $CB_2R$ [26, 37]. While $CB_2R$ are mostly found in the immune system, $CB_1R$ are highly expressed and localized to several regions of the brain, with reported expression in neurons, oligodendrocytes, astrocytes, and neural stem cells [38–46]. Owing to this abundance, the potentially greater significance of $CB_1Rs$ will be the focus of this review (Table 1).

The notably high expression of $CB_1R$ in the cerebellum, in particular on inputs into Purkinje cells from inhibitory basket and stellate interneurons and excitatory climbing fibers arising from granule cells, is indicative of the crucial role of $CB_1R$ in cerebellar function. Moreover, it has been shown that $CB_1R$ knockout mice, as well as chronic marijuana users or animals administered $CB_1R$ agonists, have clear impairment of eyeblink conditioning, an epitome of cerebellar cortex function [47–51]. 2-Arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine (AEA), 2 arachidonic acid derivatives, are the chief endocannabinoids in the brain; cerebellum $CB_1R$ are predominantly activated by 2-AG. An increase in the concentration of postsynaptic $Ca^{2+}$ either by entry via voltage-gated $Ca^{2+}$ channels or activation of type 1 metabotropic glutamate receptors brings about the release of 2-AG synthesized from diacylglycerol, a reaction catalyzed by diacylglycerol lipase-alpha in Purkinje cells, with the overall effect of activation of presynaptic $CB_1R$ [52–56]. In addition, several studies have reported the high density of $CB_1Rs$ in striatum and the presence of AEA throughout the basal ganglia, in particular in the globus pallidus and substantia nigra [31, 57, 58]. The crosstalk between dopaminergic transmission and endocannabinoids signaling in the striatum nigra is also well established and there is a growing body of evidence that $CB_1R$ activation by endocannabinoid retrograde signaling has the potential to decrease glutamate release in a dopaminergic $D_2$ receptor-dependent manner [59–61].

## Cannabinoids and Tremor in PD

PD is a progressive neurodegenerative disease affecting basal ganglia and characterized by tremor, rigidity, bradykinesia, and muscle stiffness [62–64]. The piecemeal loss of melanin-containing nigral neurons leads to aberrant dopaminergic transmission, with tremor emerging as a consequence of subthalamic overactivity [64–69]. The increase in the levels of endocannabinoids and alteration in both $CB_1R$ and $CB_2R$ expression in different stages of PD opens the possibility of manipulation of receptor function in the management of disease [64, 70]. Studies have demonstrated that, in the early stages of PD, $CB_1R$ are downregulated, while in advanced and symptomatic phases there is a switch to $CB_1R$ upregulation [71]. These findings may suggest a basis for use of cannabinoid antagonists in order to alleviate the motor deficits associated with advanced PD. Despite findings supporting this suggestion, Meschler et al. [72] failed to show the proficiency of the $CB_1R$ antagonist SR141716A (rimonabant) in the mitigation of symptoms in a nonhuman primate model of PD. In another study using tacrin, an acetylcholinesterase inhibitor, to induce Parkinsonian tremor, pretreatment with rimonabant was without significant effect on tremor bursts, whereas, in combination with the adenosine $A_{2A}$ receptor antagonist, SCH58261, a marked reduced in tremor bursts was seen [73]; however, it is of note that SCH58261 per se produced a pronounced decrease in tremor bursts. Moreover, an early clinic report suggests no advantageous effects of cannabis on tremor among 5 unresponsive patients to anticholinergics and beta blockers [74]. By contrast, a questionnaire-based study revealed a 30.6 % improvement in rest tremor in tremulous

**Table 1** A brief outlook on tremor and cannabinoid-based compounds

| Disease | Species | Drug | Dose | Effect | Comment/mechanism | Reference(s) |
|---|---|---|---|---|---|---|
| PD | | | | | | |
| Idiopathic PD | Patients unresponsive to common drugs | Marijuana cigarette | 2.9 % $\Delta^9$-THC | No changes in tremor | May be useful when anxiety is a trigger factor for tremor in patients | [74] |
| MPTP model of PD | Adult male cynomolgus monkeys (*Macaca fascicularis*) | Levonantradol ($CB_1$ agonist) | Dose range 0.01 - 0.1 mg/kg i.m. | ↓ Locomotor activities, ↑ bradykinesia, dose dependently<br>Failed to produce catalepsy | CB agonists did not induce catalepsy in primates, a finding that differs from their effects in rodents | [72] |
| | | SR141716A ($CB_1$ antagonist) | Low and high dose: 0.1–1.0 and 3.0 and 6.0 mg/kg | Failed to alleviate motor deficits | Primates may be more suitable than rodents for predicting the effects of cannabinoids and their therapeutic potential | |
| PD | L-DOPA-treated patients | WIN 55,212-2 ($CB_1$ agonist) | 5 μM | ↑ [$^{35}$S]GTPγS binding in caudate nucleus, putamen, lateral globus pallidus, and substantia nigra<br>↑ $CB_1$R binding in caudate nucleus and putamen but no changes in lateral globus pallidus and substantia nigra | More effective activation of G-protein-coupled signalling mechanisms via $CB_1$R<br>Nigro-striatal lesion →↑ $CB_1$Rs in basal ganglia in humans and nonhuman primates | [70] |
| MPTP model of PD | Marmoset with and without chronic L-DOPA treatment | | | ↑ Stimulation of [$^{35}$S]GTPγS<br>↑$CB_1$R binding in caudate nucleus and putamen<br>Following L-DOPA treatment, these parameters returned to control values. | This increase could be reversed by chronic L-DOPA therapy<br>$CB_1$R blockade might be useful as an adjuvant for treatment of Parkinsonian motor symptoms | |
| PD | Patient questionnaire-based study | Cannabis | | 45.9 % described some form of benefit<br>30.6 % improvement of rest tremor | | [75] |
| PD | Mice mutants | Deletion of genes associated with development of PD in humans: *PARK1*, *PARK2*, *PARK6* | | Biphasic pattern in CB signalling during progression of PD:<br>early stages→ desensitization/downregulation of $CB_1$R<br>Intermediate and advanced stages → upregulatory responses of $CB_1$R, possibly also $CB_2$R, and their endocannabinoid ligands | Losses may be part of the pathogenesis itself<br>$CB_1$R antagonists potentially attenuate the bradykinesia, typical of PD | [71] |
| HPD by 6-OHDA and Parkinsonian tremor by tacrine | Adult male Sprague–Dawley rats | A2A antagonists (MSX-3 or SCH58261)+$CB_1$ antagonists (rimonabant) +L-DOPA | 2 or 3 mg/kg<br>+<br>1 mg/kg<br>+<br>3 mg/kg<br>i.p. | $A_{2A}$ antagonists produce similar behavioural effects to $CB_1$ antagonists<br>Combined $A_{2A}$–$CB_1$ antagonist (SCH58261–rimonabant) →↓ only tremor bursts.<br>Rimonabant potentiates L-DOPA effects on contralateral adjusting step impairment in HPD rats | In striatal glutamatergic terminals $CB_1$-mediated inhibition of glutamate release due to $A_{2A}$ activation may also result from an interaction at second messenger level→complex relationships between $CB_1$R and $A_{2A}$R in locomotion | [73] |
| PD | Patients open-labeled study | Smoking cannabis | 0.5 g inhaled | ↓ Tremor, rigidity and bradykinesia | | [84] |
| MS | | | | | | |
| MS | Patients disabled with tremor and ataxia | Oral $\Delta^9$-THC | | 25 % patients demonstrated improved motor coordination. | | [89] |
| MS | 30-year-old patient | Marijuana cigarette | One marijuana cigarette | Hours after "experimental" cigarette, action tremor abolished<br>Acute improvement<br>Powerful beneficial effects on both spasticity and ataxia | | [92] |
| MS | Patients questionnaire-based study | Cannabis | | From 97 % to 30 %, the patients reported that cannabis improved (in descending rank order) spasticity, chronic pain of extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, | | [86] |

**Table 1** (continued)

| Disease | Species | Drug | Dose | Effect | Comment/mechanism | Reference(s) |
|---|---|---|---|---|---|---|
| | | | | bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance, and memory loss | | |
| CREAE model of MS | Mice | R(+)-WIN 55,212-2, ($CB_1R$ agonist): | 2.5 mg/kg, 5.0 mg/kg i.p.; 10.0, | Quantitatively ameliorated both tremor and spasticity | Endocannabinoid system may be tonically active in the control of tremor and spasticity. | [12] |
| | | $\Delta^9$-THC, methanandamide | 5.0 mg/kg, | | | |
| | | JWH-133 | 1.5 mg/kg i.v. | | | |
| | | SR141716A, SR144528 (CB antagonist) | 5 mg/kg i.v. | Exacerbation of both tremor and spasticity | | |
| MS | Patients | Oral cannabis extract ($n$=211) $\Delta^9$-THC ($n$=206) | 15 weeks | 48 %, 40 %, and 33 % recuperation in tremor of patients consuming cannabis extract, $\Delta^9$-THC, and placebo, respectively, but nonsignificant | | [96] |
| MS and upper limb tremor | Patients | Oral Cannador | 4 weeks | No improvement for upper limb tremor and 5 patients felt a subjective improvement of tremor whilst on active treatment. | | [99] |
| MS | 160 outpatients double-blind, randomized, placebo-controlled | Whole-plant CBME containing equal amounts of $\Delta^9$-THC and CBD | Oromucosal sprays 2.5–120.0 mg of each daily, in divided doses | No significant reduction in primary symptoms Spasticity significantly reduced | | [97] |
| MS | Patient with MS | Oral cannabis extract (Cannador) | 10 weeks | Not functionally significant, only subjective improvement in tremor | | [98] |
| | Single case report of patient | Marijuana smokers | | Acute improvement of chronic motor handicap | | |
| | 160 patients with MS | Nabiximols | | No objective improvement of tremor | | |
| Progressive EAE model of MS | Female mice C57BL/6 murine model of MS | WIN 55,512-2 (CB agonist) | 5 mg/kg i.p. | ↓ progression of symptoms (tremor, spasticity, and pain) | WIN 55,212-2 effects in EAE by activation of $CB_1$ not $CB_2$ | [93] |
| | | Antagonists of $CB_1$(rimonabant) or $CB_2$ ( AM-630) | | Reversion of positive effects of WIN 55,512-2 on neurological decline with rimonabant, not AM630 | | |
| | | HU-308 ($CB_2$ agonist) | | No positive effects on neurological decline in EAE | | |
| HD | | | | | | |
| HD | 15 neuroleptic-free patients | CBD | 10 mg/kg/day for 6 weeks p.o. | An average daily dose of 700 mg/day for 6 weeks was not symptomatically effective in neuroleptic-free HD patients | $CB_1R$ compared with other CBs CBD behaves as an antagonist in the micromolar range | [110] |
| HD | Postmortem human tissue | [3H]CP-55,940 synthetic cannabinoid | 10 nM | Relative preferential loss/dysfunction of striatal neurons projecting to lateral pallidum compared to medial pallidum | CBR-containing terminals in lateral pallidum may be affected earlier/more severely than in medial pallidum; both pallidal segments may be affected before/more severely than cell bodies or dendrites in striatum | [107] |
| HD | 58-year-old, drug-free man | Nabilone (CB agonist) | 1.5 mg | ↑ choreatic movement | Worsening effect on HD | [111] |
| 3-NP model of HD | Adult male Sprague–Dawley rat | AM-404 (endocannabinoid uptake inhibitor) | 10 mg/kg i.p. | ↓motor disturbances observed in the early phase of hyperactivity induced recovery in GABA and dopamine deficiency induced by toxin in the basal ganglia | Biphasic motor disturbances, with an early (1–2 week) hyperactivity followed by a late (3–4 weeks) motor depression and a loss of $CB_1R$ in the basal ganglia of HD rats | [104] |
| HD | 44 randomized patients | Nabilone | 1 or 2 mg | A treatment difference of 0.86 (95 % CI –1.8 to 3.52) for total motor score; 1.68 (95 % CI 0.44–2.92) for chorea | Change in motor symptoms of HD was small Did not exacerbate chorea | [114] |

**Table 1** (continued)

| Disease | Species | Drug | Dose | Effect | Comment/mechanism | Reference(s) |
|---|---|---|---|---|---|---|
| 3-NP and malonate model of HD | Adult male Sprague–Dawley rats | $\Delta^9$-THC–CBD-enriched botanical extracts combined in a ratio of 1:1 | 4.63 mg/kg | ↓3-NP-induced GABA deficiency, loss of Nissl-stained neurons, downregulation of $CB_1R$ | These effects are probably related to antioxidant and CBR independent properties of both phytocannabinoids | [115] |
| | | CB antagonists: SR141716 AM630 | 1 mg/kg | Positive effect of phytocannabinoids, not reversed by CB antagonists | | |
| 3-NP model of HD | N171-82Q transgenic model | Genetic deletion of $CB_1R$ | | Worsened motor performances in N171-82Q mice and ↑susceptibility to 3-NP toxin for HD induction | | [121] |
| Ataxia | | | | | | |
| Patients with MS disabled by tremor and ataxia | 8 patients | CB agonists: $\Delta^9$-THC | Dose range: 5–15 mg p.o. | two patients demonstrated improved motor coordination | | [89] |
| Patients with MS | Clinical rating, EMG of leg flexor reflexes and electromagnetic recording of hand action tremor | Marijuana | Cigarette | Acute improvement of chronic motor handicaps | | [92] |
| Microinjection via implanted stainless steel guide cannulas | Male CD-1 mice | Synthetic CB agonists: CP55,940 and HU-210 $CB_1$ antagonist: SR141716A | intracerebellar (i.c.b.) (5–25 μg) (1.56–6.25 μg) (25 μg) | Dose-dependent motor incoordination elicited by HU-210 (6.25 μg) and CP55,940 (20 μg) was significantly blocked by SR141716A (25 μg) | Cannabinoid-induced motor impairment occurs by activation of $CB_1$ receptor in cerebellum | [117] |
| Model of motor impairment | Male ICR albino mice | $CB_1$ agonists: CP55940, WIN 55,212-2, $\Delta^9$-THC AEA: 2 AEA analogs (ACEA and ACPA) $CB_1$ antagonist: SR141716 | (1, 3) 10, (30, 100) mg/kg i.p. (3-10) mg/kg i.v. (1, 5) mg/kg i.p. | All $CB_1$ receptor agonists → ↑ in gait width (truncal ataxia) and number of slips in the bar cross test (motor incoordination) Pretreatment with SR141716 → ↓ both the change in gait width and number of slips induced by CP55940 and AEA Neither cannabidiol nor WIN 55,212-2 affected measures | This effect is mediated by the $CB_1$ receptor The assays used in this study are specific for cerebellar-mediated behavioral deficits, so these deficits are not mediated by the basal ganglia or cannabinoid-induced alterations in nigrostriatal dopaminergic transmission | [118] |
| Animal models of cerebellar ataxia display | "Ducky" $du^{2J}$ mouse | | | $Du^{2J}$ ataxia model is associated with deficient $CB_1$ signalling in the cerebellar cortex, putatively linked with compromised $Ca^{2+}$ channel activity and the ataxic phenotype | | [119] |

PD = Parkinson's disease; $\Delta^9$-THC = $\Delta^9$-tetrahydrocannabinol; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; CB = cannabinoid; i.m. = intramuscularly; L-DOPA = levodopa; GTPγS = nonhydrolyzable G-protein-activiating analog of guanosine triphosphate; $CB_1R$ = cannabinoid receptor type 1; 6-OHDA = oxidopamine; $A_{2A}$ = adenosine $A_{2A}$ receptor; MSX-3 = Selective $A_{2A}$ adenosine receptor antagonist; i.p. = intraperitoneally; HPD = Hemi-Parkinson's disease; $A_{2A}R$ = $A_{2A}$ receptor; MS = multiple sclerosis; CREAE = chronic/relapsing experimental allergic encephalomyelitis; i.v. = intravenously; CBME = cannabis-based medicinal extract; CBD = cannabidiol; EAE = experimental autoimmune encephalomyelitis; HD = Huntingdon's disease; p.o. = per os (i.e., orally); 3-NP = 3-nitropropionic acid; GABA = γ-aminobutyric acid; CI = confidence interval; EMG = electromyography; (i.c.b.) = intracerebellar; ICR = Institute for Cancer Research; AEA = N-arachidonoylethanolamine; ACEA = Arachidonoyl 2' -chloroethylamide; ACPA = Arachidonoyl Cyclopropylamide

patients with PD [75]. A plausible argument for using cannabinoid agonists as therapeutic agents has arisen from studies describing the inhibitory effect of $CB_1R$ activation on glutamate release and its capability to oppose subthalamonigral neuronal overactivity and subsequently reduce tremor [64, 76, 77]. It has also been suggested that cannabinoid agonists and endocannabinoids can block dopamine transporters and thereby inhibit dopamine reuptake to ameliorate dyskinesia [78–80]. However, there are other studies asserting no beneficial effects of cannabinoid agonists in alleviation of motor symptoms [75, 81–83].

Unfortunately, there are currently only few double-blind controlled studies and those that have been performed are often paradoxical. In a recent small, open-labeled observational study, the efficacy of cannabis treatment on patients who had experienced severe PD-related pain and tremor, and whose symptoms were insufficiently controlled with current anti-Parkinson medications, was assessed [84]; the results indicated a significant improvement in tremor and rigidity, with a lesser beneficial effect on bradykinesia, among cannabis smokers. Currently, an observational prospective clinical trial is underway to scrutinize the impact of cannabis on PD tremor (ClinicalTrials.gov identifier: NCT02028858); such trials should help advance, and resolve, controversies in this field. Despite these conflicting results, cannabinoid-based compounds should not be neglected as a treatment strategy. It seems that alterations to the endocannabinoid system may play a role in Parkinsonian tremor pathogenesis and that more studies are requisite to consider a further range of individual cannabinoids as potential therapeutic agents for managing signs and symptoms of PD, in particular, tremor.

## Cannabinoids and MS-related Tremor

There is much anecdotal evidence that patients self-medicate with marijuana with the intention of palliating pain, tremor, spasticity, ataxia, and other symptoms associated with MS, an autoimmune disease typified by demyelination and remyelination, and associated with neuroaxonal damage and inflammation [67, 69, 85, 86]. More recent controlled studies, both in animal models of MS and in humans, have begun to validate these preclinical and uncontrolled observations. Involvement of the endocannabinoid system acting at $CB_1R$ in the pathogenesis of MS have been supported by several studies [87–90]. There are now several lines of evidence indicative of therapeutic potentials of cannabinoids in the control of MS-related symptoms, including tremor, which remains difficult to manage with current medications (e.g., carbamazepine, propranolol, primidone, and gluthetimide) [12, 89, 91, 92]. Following this premise, De Lago et al. [93] have shown that the nonselective cannabinoid agonist WIN 55,212-2 ameliorated neurological disability, tremor, and spasticity in the chronic relapsing experimental autoimmune encephalomyelitis murine model of MS [92]. Correspondingly, this study revealed the prominent role of $CB_1R$ activation in the relief of tremor and spasticity, as a selective $CB_1R$, but not a $CB_2R$, antagonist reversed the positive effects of preadministered cannabinoids; moreover, no beneficial effects were observed by administering a selective $CB_2$ agonist [93, 94]. An earlier study reported that cannabinoid agonists $\Delta^9$-THC, methanandamide, R(+)WIN 55,212-2, and JWH-133 all diminished tremor and spasticity in the experimental autoimmune encephalomyelitis model, and that aggravation of the symptoms occurred after using $CB_2R$ and, in particular, $CB_1R$ antagonists [12].

There is also an animal study that supports previous findings which report that chronic, but not acute, $\Delta^9$-THC-rich extracts are effective in reducing tremor and spasticity [95]. The "cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis" (CAMS) study, where 611 of 630 patients were followed, reported 48 %, 40 %, and 33 % recuperation in tremor of patients consuming cannabis extract, $\Delta^9$-THC, and placebo, respectively; however, the difference in perception of tremor improvement was not statistically significant [96]. A double-blind randomized placebo controlled study failed to show any favorable effects of a cannabis-based medicinal extract on tremor in a subgroup of 13 patients [97, 98]. In addition, although placebo recipients showed faster finger tapping than that of cannabis extract recipients in a randomized double-blind crossover trial amongst 14 tremulous patients, the study was unable to show any overall marked improvement on measures of objective tremor [99]. In a systematic review published by Koppel et al. [100], oral cannabis extract and $\Delta^9$-THC was considered, at present, "probably ineffective" and Sativex (nabiximols) "possibly ineffective" for easing MS-related tremors [100]. Although a decrease in $CB_1R$ density has been found in caudate–putamen and cortical regions, there are still lack of convincing data on changes to $CB_1R$ and $CB_2R$ expression and endocannabinoid transmission in both animals and postmortem brain of patients suffering from MS [12, 101].

## Cannabinoids and HD-related Tremor

HD is an autosomal dominant, progressive neurodegenerative disorder primarily affecting cortical and striatal neurons [102, 103]; HD is characterized by chorea, that is, jerky involuntary movements (from the Greek word *khoreia* meaning "dancing in unison"). The loss of $CB_1R$ during the progression of HD, most specifically in the lateral pallidum, in transgenic mouse models of HD and in postmortem basal ganglia of patients who suffered from HD, represents a possible justification to investigate the use of cannabinoid agonists in HD [104–107]. While a beneficial response in reducing chorea has been reported for CBD [108], a controlled clinical trial among 15

patients with HD showed no significant improvements in chorea severity after 6 weeks of CBD administration at an average daily dose of 700 mg/day [109, 110]. In 2 uncontrolled single-patient, single-dose studies, nabilone produced opposing effects, worsening the symptoms and increasing choreatic movements in one study, but improving symptoms in the other [111–113]. A recent randomized, double-blind, placebo-controlled, crossover study also indicated the effectiveness of nabilone in the improvement in chorea [114]. It should be pointed out that none of these studies has investigated disease progression and they have all used a single cannabinoid. Therefore, data from animal models suggest either that combinations of different cannabinoids or a broad-spectrum cannabinoid may be needed to justify the lack of positive findings in some of the mentioned studies [115, 116].

## Ataxia

Ataxias are a group of related neurological movement disorders that affect coordination, balance, and speech, and can also be associated with tremor. It is well known that cannabinoid agonists can induce motor dysfunction in the cerebellum to give an ataxic phenotype in animals, with effects ameliorated by selective $CB_1R$ antagonists [117, 118]. To date, there have been no published clinical trials on effects of cannabinoids in ataxia and potential effects on ataxia are confined to case report data in patients with MS with associated ataxia. Here, oral $\Delta^9$-THC or marijuana have been reported to improve motor coordination in some patients with MS [89, 92]. These reports contrast with the clear exacerbating effects of $CB_1R$ agonists in animals and suggest that investigations with different cannabinoids in patient populations with specific ataxias are needed. In one preclinical model, namely, the "ducky" *du*$^{2J}$ mouse model of ataxia and absence epilepsy, it was found that the prominent $CB_1R$-mediated inhibition of GABAergic transmission at interneuron–Purkinje cell synapses seen in the wild type was completely absent in heterozygous and homozygous *du*$^{2J}$ mice, despite $CB_1R$ expression being unchanged [119] . *du*$^{2J}$ mice are deficit in the auxiliary $Ca^{2+}$ channel subunit $\alpha 2\delta 2$, and these data are consistent with this deficit leading to aberrant $CB_1R$ signaling downstream of receptor activation; it is also possible that deficits in endocannabinoid modulation of inhibitory transmission in the cerebellum contribute to the ataxic phenotype seen here.

## Concluding Remarks

Cannabinoids, proposed to act predominantly via $CB_1R$ and $CB_2R$ activation, have been evaluated for different medical purposes. Cannabinoid receptors and endocannabinoids are highly abundant in the brain areas involved in the management of motor function, and their significant role in modulating many motor functions has been detailed. Although the exact molecular mechanisms of cannabinoid signaling in the pathogenesis of motor-related diseases has not been fully elucidated, and there are significant gaps in our understandings of their influence on motor pathways, medical cannabis appears to have benefits among some patients enduring tremor-associated diseases. However, no studies have so far investigated the role of cannabinoids in essential tremor. At present, despite much anecdotal evidence, observations from case studies and controlled human trials remain poorly matched with those in animal models of diseases. In order to better bridge this gap, it will be important to elucidate mechanisms of cannabinoid action and use comprehensive controlled studies to determine the impact of different cannabinoid-based compounds on tremor-related diseases in both animal models and humans. Furthermore, many clinical studies have reported psychoactive side effects of cannabinoids and hence their introduction in clinical use remains somewhat controversial. Therefore, there is a need to improve and develop novel therapeutic strategies using cannabinoid-based medicines with fewer side effects. In this regard, non-$\Delta^9$-THC cannabinoids may provide an attractive alternative. Moreover, while the above mentioned studies have largely focused on exogenous cannabinoid and endocannabinoid effects on $CB_1R$ in the central nervous system, it is important to point out that cannabinoid compounds may also act at alternative molecular targets [120]; in particular, the major phytocannabinoid, CBD, has only low, pharmacologically irrelevant, affinity at $CB_1R$ and is not associated with psychoactive effects. CBD was recent given orphan drug status for Dravet syndrome and warrants further investigation here, as do other non-$\Delta^9$-THC phytocannabinoids, to determine which may be friends and which may be foes in the aim of combating tremor. Given the foregoing considerations, it is reasonable to conclude that cannabinoids represent potential candidates for the management of tremor in some patients with motor-related diseases but that more studies should be done in order to elucidate alterations in cell signaling in both basal ganglia and cerebellum of animal models treated with cannabinoids with the aim of reducing tremors.

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