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The Therapeutic Potential of Cannabinoids for Movement Disorders

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Abstract

Background—There is growing interest in the therapeutic potential of marijuana (cannabis) and cannabinoid-based chemicals within the medical community and particularly for neurologic conditions. This interest is driven both by changes in the legal status of cannabis in many areas

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and increasing research into the roles of endocannabinoids within the central nervous system and their potential as symptomatic and/or neuroprotective therapies. We review basic science, preclinical and clinical studies on the therapeutic potential of cannabinoids specifically as it relates to movement disorders.

Results—The pharmacology of cannabis is complex with over 60 neuroactive chemicals identified to date. The endocannabinoid system modulates neurotransmission involved in motor function, particularly within the basal ganglia. Preclinical research in animal models of several movement disorders have shown variable evidence for symptomatic benefits but more consistently suggest potential neuroprotective effects in several animal models of Parkinson's (PD) and Huntington's disease (HD). Clinical observations and clinical trials of cannabinoid-based therapies suggests a possible benefit of cannabinoids for tics and probably no benefit for tremor in multiple sclerosis or dyskinesias or motor symptoms in PD. Data are insufficient to draw conclusions regarding HD, dystonia or ataxia and nonexistent for myoclonus or restless legs syndrome.

Conclusions—Despite the widespread publicity about the medical benefits of cannabinoids, further preclinical and clinical research is needed to better characterize the pharmacological, physiological and therapeutic effects of this class of drugs in movement disorders.

Keywords

cannabinoids; cannabis; movement disorders; Parkinson's disease; Huntington's disease

Introduction

Cannabis (marijuana) has long been used for medicinal purposes in many cultures as well as for spiritual and recreational purposes due to its psychoactive properties. Over 60 pharmacologically active compounds or phytocannabinoids have been isolated from cannabis including Δ9-tetrahydrocannabinol (THC), the primary psychotropic compound, and cannabidiol (CBD), a nonpsychoactive chemical with potential therapeutic properties.[1] Nearly all cannabis strains are derived from two cannabis species, sativa and indica. Sativa strains have higher THC concentrations and produce more euphoria, whereas indica strains have more CBD and have more sedating, anti-emetic, and analgesic properties.

Over the past three decades, cannabinoid receptors and endogenously produced cannabinoids (eCBs) have been discovered in a wide range of tissues including peripheral nerves and the central nervous system (CNS). The endocannabinoid system (ECS) has been implicated in a broad range of physiological functions, including cognition, mood, motor control, feeding behaviors, and pain.[2–5] Consequently, cannabinoid-based therapies have been studied for a variety of illnesses.[6] Cannabinoid-based medicines, such as nabilone, dronabinol, and Sativex®, are now approved for clinical indications, including pain, anorexia, spasticity, and chemotherapy-induced nausea and Epidiolex™ recently obtained orphan drug status for Dravet syndrome. [6, 7]

Preclinical research suggests that cannabinoids have symptomatic and neuroprotective potential for a variety of neurologic conditions, including movement disorders. The American Academy of Neurology (AAN) Guideline Development Subcommittee

systematically evaluated the published clinical evidence and concluded that oral cannabis extract is effective in treating multiple sclerosis (MS) related spasticity and central pain or painful spasms, and that cannabinoid-based therapies are probably ineffective in treating levodopa-induced dyskinesias (LID) in Parkinson's disease (PD) or tremor and are of unknown efficacy for Huntington's disease (HD), tics or dystonia.[8] Our objective is to provide a more in-depth review of preclinical and clinical studies related to the therapeutic potential of cannabinoids for movement disorders.

PRECLINICAL RESEARCH

Endocannabinoids and the Basal Ganglia

The primary cannabinoid receptor subtypes are cannabinoid receptors type 1 (CB_1) and type 2 (CB_2). CB_1 receptors are highly expressed in the CNS, especially the basal ganglia, and also identified in almost all peripheral tissues and cell types.[9] CB_2 receptors are expressed primarily in the immune system, where they modulate inflammation, but are also expressed in the CNS, particularly in neurons within the dorsal vagal motor nucleus, the nucleus ambiguous, the spinal trigeminal nucleus, and microglia.[10, 11] Recently, CB_2 receptors were found in the basal ganglia and studies suggest that impairment of these receptors may be associated with dyskinesias [12] While most actions of cannabinoids are related to CB_1 and CB_2 receptors, other receptor types have been described, including the transient receptor potential vanilloid type 1 (TRPV1) cation channel,[13] the GTP-binding protein-coupled receptor GPR55,[14] the abnormal-CBD receptor,[15] and the peroxisome-proliferator-activated receptor (PPAR).[16]

eCBs are lipophilic compounds that demonstrate varying degrees of affinity for G-protein coupled cannabinoid receptors and include anandamide and 2-arachidonoglycerol (2-AG; see Table 1). eCBs primarily function through retrograde signaling, wherein post-synaptic activity leads to eCB production and release with backward transmission across the synapse to depress presynaptic neurotransmitter release.[5] The ECS may also support synapse formation and neurogenesis.[5] Within the basal ganglia, eCBs and CB_1 receptors tend to increase GABAergic and inhibit glutamatergic transmission.[9] eCBs also tend to inhibit dopamine release through GABAergic mechanisms.[17] eCBs are not stored and are quickly degraded after exerting a transient and localized effect. Removal of eCBs from the extracellular space occurs through cellular uptake and metabolism with anandamide degraded primarily by fatty acid amide hydrolysis (FAAH) and 2-AG degraded by monoacylglycerol lipase.[18]

Neuroprotective Potential of Cannabinoids

Several studies in animal models of both PD and HD suggest that cannabinoid-based therapies may attenuate neurodegeneration (Table 2). Indeed, on October 7, 2003, U.S. Health and Human Services was granted U.S. Patent 6630507, which lists the use of cannabinoids found within the cannabis sativa plant as useful in certain neurodegenerative diseases such as PD, Alzheimer's disease and dementia caused by human immunodeficiency virus.[141] Cannabinoids may offer neuroprotection through both receptor-mediated and receptor-independent mechanisms. Cannabinoids are capable of reducing oxidative damage

by acting as scavengers of reactive oxygen species (ROS) and enhancing endogenous antioxidant defenses.[19] This property appears to be independent of CB_1 and CB_2 receptor modulation and restricted to certain cannabinoids, including CBD, THC, cannabinol, CP55,940, and the anandamide analogue AM404.[20–22] CB_2 agonists exert anti-inflammatory effects by inhibiting reactive microglia and cytokine release.[20, 23–25] Lastly, CB_1 agonists reduce excitotoxicity by suppressing glutamatergic activity, subsequent calcium ion influx, and nitric oxide production.[26, 27] However, in one study, both a CB_1 agonist, THC, and a selective CB_1 antagonist, rimonabant, exacerbated malonate-induced striatal lesions.[28]

Parkinson's disease

Experimental models of PD show increased ECS activity in the basal ganglia, including increased CB_1 mRNA levels, CB_1 activity, anandamide levels, and decreased cannabinoid clearance.[29–33] These changes appear to be associated with movement suppression and may be reversed by chronic levodopa treatment.[29, 35] Importantly, many cannabinoids demonstrate neuroprotective effects in several models of PD (Table 2). These effects appear to be mediated by both CB receptor dependent and independent mechanisms including antioxidant effects, reduced microglia activation, and modulation of glial-neuron interactions.[20,24,67,121]

Animal studies further suggest that cannabinoids may improve motor symptoms of PD and LID, but results are variable (Table 3). CB_1 agonists inhibit basal ganglia dopamine release and are there for expected to be ineffective in alleviating PD motor symptoms. Indeed, CB_1 agonists have been shown to exacerbate bradykinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primates.[38] However, CB_1 agonists have also been reported to improve motor impairments, possibly through nondopaminergic mechanisms including interactions with adenosine A_2A receptors.[39–44] Studies of CB_1 antagonists are more consistent in improving motor symptoms without increasing dyskinesias.[45–49] These effects appear to involve nondopaminergic mechanisms including enhanced striatal glutamate release and may be greater in animals with more severe striatonigral degeneration.[29, 46, 47] Potential explanations for the therapeutic variability of CB-based compounds include differences in lesion severity, trial design, dose, and gender.[46, 48, 49] Different CB_1 modulators may also exhibit functional selectivity for different G proteins or subpopulations of CB_1 receptors, a phenomenon referred to as biased agonism.[50, 51]

While CB_1 and CB_2 receptors are decreased in the basal ganglia of dyskinetic animals, it is not known whether this is compensatory or causal.[12] Animal studies suggest cannabinoid-based therapies may improve LID without worsening motor control. Interestingly, these effects are reported for both CB_1 agonists[52] and antagonists[45], although these effects are not seen in all studies and higher doses of CB_1 agonists may impair motor function suggesting that CB_1 agonist effects on LID are related to general motor suppressant effects.[53–55] Other CB receptors may also be involved in LID as URB597 (a FAAH inhibitor which increases anandamide levels) did not affect LID as monotherapy but did improve LID when co-administered with a TRPV1 antagonist, suggesting that TRPV1 and CB_1 may have opposing effects.[54]

Huntington's Disease

Experimental animal models indicate that HD is associated with early and widespread reductions in the ECS, particularly CB_1 receptors in the striatum.[62,63] CB_1 receptors mediate brain-derived neurotrophic factor expression and CB_1 receptor loss is associated with exacerbation of symptoms, neuropathology, and molecular pathology in the striatum. Moreover, cannabinoid-based therapies generally show neuroprotection in several animal models through both CB receptor mediated and independent effects (Table 2).[145,124,127] Caution is warranted as several studies using identical cannabinoids and models showed no benefit or even exacerbation of neurotoxicity.[67,28,126] Therapeutic studies of cannabinoid-based agents in HD animal models suggest that CB_1 and endovanilloid receptor agonists[28, 66] and anandamide reuptake inhibitors[67] are capable of alleviating hyperkinesia (Table 3). This therapeutic potential is likely to be realized in early phases of HD because of progressive loss of CB_1 receptors in advanced stages.[68]

Dystonia and Tremor

It has been hypothesized that CB_1 agonists reduce overactivity of the globus pallidus interna (GPi) and improve dystonia by reducing GABA reuptake.[73] In support of this idea, the CB_1 and CB_2 agonist WIN55,212-2 produces antidystonic effects in a mutant hamster model of dystonia, increases the antidystonic efficacy of benzodiazepines and is reversed by rimonabant, a selective CB_1 antagonist.[74, 75] Animal models suggest that cannabinoids may reduce MS-related tremor, an effect that appears to be selectively mediated by CB_1 receptors.[92]

CLINICAL RESEARCH

Parkinson's Disease

Compared to control subject, humans with PD show elevated cerebrospinal fluid levels of anandamide and autopsied brains of PD patients show decreased CB_1 mRNA expression in the basal ganglia.[34, 36] It is not clear whether these discrepancies reflect medication effects, down-regulation from increased agonist activity or differences in disease severity. Regarding non-motor symptoms, one study reported CB_1 receptor gene (CNR1) polymorphisms may influence depression risk in PD.[37]

Observational and uncontrolled studies suggest cannabinoids may improve PD motor symptoms.[56–58] In a survey of PD patients (N = 339) in the Czech Republic, 25% of respondents reported using cannabis and 46% of these described some benefit; 31% reported improvement of rest tremor, 45% of bradykinesia, and 14% of LID.[57] Notably, there was a 54% response rate to this survey suggesting a potential for respondent bias. A small (N=22) open-label study assessing motor exam 30 minutes after smoking cannabis also reported improvements in tremor, rigidity, bradykinesia, pain and sleep.[58] Regarding nonmotor symptoms, a small (N=6) 4-week open-label study of CBD for psychosis in PD found improvements on the Brief Psychiatric Rating Scale and Parkinson Psychosis Questionnaire and another case series (N=4) reported benefits for rapid eye movement sleep behavior disorder.[56,139] However, a case series of 5 patients found no benefit for tremor following a single administration of smoked cannabis.[138]

In contrast, 4 controlled clinical studies of cannabinoids reported no benefit for motor symptoms, mixed results regarding LID and quality of life.[59–61, 140] (Table 4) A small (N=5) randomized, double-blind, placebo-controlled crossover trial, assessed the efficacy of 0.03 mg/kg nabilone, a CB_1 and CB_2 agonist for LID given in a split dose 12 and 1 hour prior to a levodopa challenge.[61] They found a significant reduction in LID versus placebo on the Rush Dyskinesia Disability Scale and total LID time. Nabilone did not diminish the antiparkinsonian actions of levodopa or improve parkinsonian symptoms although 2 patients reported improvements in painful off-period dystonia. A larger (N=17) 4-week randomized double-blind crossover study of twice daily Cannador, an oral cannabis extract containing 1.25 mg CBD and 2.5 mg THC, titrated Cannador up to 0.25 mg/kg THC for LID.[59] Although the blinding seemed to be compromised (71% correct identification of treatment), Cannador failed to improve LID on multiple outcomes, including a non-significant worsening on their primary outcome (UPDRS dyskinesia items) and the Rush Dyskinesia scale. There were no significant changes for other secondary outcomes including motor symptoms (Part 3 UPDRS), quality of life (PDQ-39) or sleep. Another small (N=8) 16-day randomized placebo-controlled trial assessing the efficacy of 20 mg daily oral rimonabant (CB_1 antagonist) showed no effect on parkinsonian motor symptoms or LID as measured by the UPDRS and a standardized videotape procedure.[60] Examination of data suggested a trend towards worsening in motor scores but the small sample size and other methodological issues prevent any meaningful conclusions. Most recently, 21 PD patients were randomized to placebo, CBD 75mg/day or CBD 300 mg/day for a 6-week trial.[140] No significant changes were found for the total UPDRS or any subscales or measures of neuroprotection (serum brain derived neurotrophic factor levels or putamen magnetic resonance spectroscopy). Improvements were noted for the total PDQ-39 score and stigma and activities of daily living subscores for the CBD 300 mg/day group. Despite the low sample size and quality of these studies, the data suggest cannabinoid agonists and antagonists are probably ineffective for both LID and motor symptoms although further study using different doses, formulations or target symptoms (e.g. dystonia, psychosis, sleep) may be justified. While there were no serious adverse events reported, side effects included hypotension, vertigo, visual hallucinations, dizziness and somnolence.

Huntington's Disease

Post-mortem human studies and PET imaging studies using a CB1 ligand support experimental HD models in demonstrating early and marked decreases in both subcortical and cortical CB1 receptors.[64,65] Clinical research of cannabinoids for HD symptoms are inconclusive. (Table 4) Case reports using nabilone, a CB_1 agonist, reported worsening of chorea severity in one patient and benefits for chorea and irritability in another.[69, 70] A small (N=15) randomized double-blind placebo-controlled crossover trial assessed CBD capsules (10 mg/kg divided in twice daily doses) given for 6-weeks for chorea as measured by the Marsden and Quinn chorea severity scale.[71] This study found small and statistically insignificant differences between groups on primary and secondary outcomes, including patient global impressions. A larger (N=37) 5-week double-blind placebo-controlled randomized cross-over trial assessed nabilone titrated to 1 or 2 mg given twice daily for 5 weeks on the total motor score of the Unified Huntington's disease rating scale (UHDRS).[72] Change in total UHDRS did not differ between groups. However, statistically significant

improvements were noted for the UHDRS chorea scale and the neuropsychiatric inventory with a trend for improvement on the UHDRS behavior score. There were no statistical differences reported between the 1 and 2 mg. Notably, one patient withdrew due to severe sedation. These results are encouraging and suggest a need for larger controlled trials. A phase II (N=25) double-blind placebo-controlled randomized clinical trial is examining the safety and neuroprotective efficacy of nabiximols, a combination of CBD and THC, using clinical and biomarker (cerebrospinal brain-derived neurotrophic factor) outcomes, but results are not yet available (NCT Identifier: NCT01502046).

Dystonia

While case reports of smoked cannabis for generalized dystonia in Wilson's disease,[76] idiopathic hemidystonia,[77] and a case series of 5 patients with dystonia secondary to diverse causes treated with oral CBD (100–600 mg daily)[78] suggest cannabinoids may alleviate dystonia, 2 small randomized placebo-controlled clinical trials for dystonia showed no effect (Table 4). Notably, the case series reported exacerbated hypokinesia and tremor in 2 patients and other mild side effects including hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation.[78] A small (N=13) randomized double-blind placebo-controlled cross-over trial tested a single dose of 0.03 mg/kg nabilone or placebo on patients with medication refractory focal or generalized dystonia using the Burke-Fahn-Marsden dystonia scale.[73] They reported no significant differences between groups at 60, 120 or 180 minutes, including when separating generalized from segmental patients. 4 patients reported a subjective improvement lasting 3 days after nabilone and 2 patients withdrew secondary to hypotension and sedation. A second small (N=7) randomized placebo-controlled crossover trial assessed 7.5 mg dronabinol, a CB_1 and CB_2 agonist, given twice daily for 2 weeks in patients with cervical dystonia using the Toronto Western Hospital Spasmodic Torticollis Rating Scale (TWSTRS).[79] There were no significant differences noted on TWSTRS (total or subscales) or subjective ratings. One subject withdrew secondary to insomnia and sensation of heart racing, and all but one subject reported mild side effects including lightheadedness, hypotension, vertigo and dry mouth.

Tics and Tourette Syndrome

Case reports of smoked cannabis,[80] oral THC,[81–84] and case series of smoked cannabis (N = 3)[85] suggest that cannabinoids may be beneficial for tics in patients with Tourette syndrome (TS). Similarly, a survey of 64 TS patients found that 17 (27%) had tried marijuana and 14 of them (82%) found it helpful for tics and behavioral disturbances.[86] Although only 2 controlled trials have assessed the efficacy of cannabinoids for tics, the results support these uncontrolled clinical reports. A small (N=12) randomized double-blind placebo-controlled single-dose crossover trial assessed a single dose of 5–10 mg oral THC (dose based on body weight and prior marijuana use) for tics in TS using the Tourette Syndrome Symptom List (TSSL).[87] Tics and obsessive compulsive behavior significantly improved on the TSSL with statistically significant improvements or trends towards improvement in other secondary outcomes including the Yale Global Tic Severity Scale. Mild side effects noted by 5 patients included headache, dizziness, nausea and cognitive changes. Another small (N=17) 6-week randomized placebo-controlled parallel group trial of 6-weeks 10 mg daily orally-administered THC assessed tic reduction in TS patients using the Tourette Syndrome

Clinical Global Impression scale (TS-CGI).[88] This study also found significant improvements in the primary and most secondary outcomes. A related study from the same cohort reported no significant change in neuropsychological performance with THC treatment.[89] Limitations of these studies include small sample size, short treatment period, multiple comparisons, fixed or single dose approach, potential blinding issues and possible selection bias. Given these limitations, AAN evidence-based systematic review, as well as a recent Cochran review on the efficacy of cannabinoids in TS, state that there is presently "insufficient evidence to support or refute the clinical use of THC, nabilone, or cannabis for tics".[8, 90] However, in treatment resistant adult patients, THC may have therapeutic effects and is recommended by some experts.[91] Positive results of preliminary studies warrant validation of the efficacy and safety of THC for tics in larger randomized clinical trials.

Multiple Sclerosis-related Tremor

A small (N=8) case series of 5–15 mg oral THC given 4 times a day reported objective improvement in tremor in 2 patients and subjective improvement in 5.[93] However, subsequent clinical trials assessing the efficacy of cannabinoids for MS-related tremor failed to show benefit. A small (N=13) 6-week randomized double-blind placebo-controlled trial assessed Cannador dosed up to 0.125 mg/kg THC twice daily for patients with MS-related tremor.[94] There were no statistically significant effects as measured by a tremor index, the Nine-Hole Peg Test of manual dexterity, spiral drawings or other objective measures although 5 patients reported subjective benefits. Notably, 9 of 13 patients correctly guessed their treatment group and 10 reported mild adverse effects including cognitive changes, drowsiness, lightheadedness and dry mouth. A large (N=337) 8-week double-blind, randomized placebo-controlled trial of up to 24 actuations per day of oral nabiximols spray (65 mg THC, 60 mg CBD), evaluated tremor as a secondary outcome with an index score and patient global impression of change and reported no effect on tremor.[95] Another large (N=391) 15-week randomized placebo-controlled trial assessing the efficacy of oral THC (marinol) versus oral cannabis extract (both dosed up to 12.5 mg given twice daily) versus placebo showed no difference in patient ratings of tremor as a secondary outcome.[96] Given the consistent lack of response to cannabinoids in patients suffering from MS-related tremor, AAN evidence-based guidelines state THC and oral cannabis extract are probably ineffective for reducing MS-related tremor and nabiximols are possibly ineffective.[8] To our knowledge there have been no studies of CB-based treatments for essential tremor or other tremor types.

Other Movement Disorders

There have been no published clinical trials of cannabinoids for ataxia, myoclonus or restless legs syndrome. Two case reports suggest ataxia (in combination with spasticity) in MS may improve following smoked cannabis or oral THC and a survey of 112 MS patients reported some individuals noting improvement in balance.[93, 97, 98] Marijuana may be effective for psychogenic symptoms as illustrated by a report by Sanjay Gupta, called "Weed", which featured a 19 year old young man who after 7 minutes of "convulsing" with "myoclonus – diaphragmatic flutter", resembling psychogenic tic or tremor, had a sudden resolution of the movement, respiratory and speech disorder within seconds of smoking marijuana.[99,142]

Adverse Effects and Risk of Addiction

While cannabinoids appear to be well tolerated when used in moderation, AEs are clearly a major concern. In the systematic review of CB studies conducted by the AAN 6.9% (95% CI 5.7%–8.2%) of participants stopped their medication due to AEs.[8] AEs include ataxia, nausea, impaired short-term memory, stroke, cognitive impairment, dry mouth, suicidal ideation, hallucinations, dizziness, fatigue, behavioral or mood changes, impaired motor skills, increased weakness, heart rate and appetite.[8, 100, 101] Marijuana use is also associated with an increased risk of chronic anxiety, depression and psychosis, though causality has not been established.[102] Except for ataxia, there have been no documented cases of movement disorders induced by cannabis use. However, there has been one case report of propriospinal myoclonus possibly induced by cannabis,[103] but this form of myoclonus is often of psychogenic origin.[104]

It is important to note that side effects, as well as therapeutic effects, vary depending on the CB(s), concentration of CB(s), or ratio of CBs in formulations.[105] Smoking cannabis has been associated with lung cancer risk so future trials should focus on other methods of ingestion, although oral administration is also problematic due to deposition of cannabinoids into fatty tissue, from which they are released slowly, causing variability in plasma concentrations.[106, 107]

There is also an important risk of abuse with marijuana and cannabis-based drugs.[108] Studies of marijuana outside of the medical context estimate 9% of persons using cannabis may become addicted and experience symptoms of withdrawal after quitting the drug.[109] The mechanism of abuse in marijuana users is not well understood but may involve blunted dopamine reactivity. This is supported by the observation that marijuana abusers, compared to healthy controls, showed markedly blunted dopamine responses when challenged with methylphenidate and that PET scans using [11C] raclopride, a D2 ligand, show dopamine in ventral striatum of marijuana abusers was inversely correlated with addiction severity and craving.[110] It is likely that patients using medical formulations may be at lower risk, due to lower doses, use related to a specific indication, and formulations with a lower concentration of THC, the key component responsible for the dependence potential of cannabis.[111] Cannabis is generally safe in overdose although illicit synthetic cannabinoids have been associated with severe medical and psychiatric complications.[112, 113] Finally, epidimiological studies suggest that cannabis may be a “gateway drug” as its use is associated with later use of other illicit substances.[143] While the causal role and mechanisms of the gateway idea are still debated, it is prudent for future clinical trials to monitor for current and subsequent use of other illicit substances.[144]

Discussion and Directions for Future Research

Although the number of preclinical studies of cannabinoids for movement disorders has rapidly increased in the last three decades, there are marked gaps in our knowledge about their effects on motor pathways. There are also marked discrepancies and conflicting results in preclinical studies including the precise effects of cannabinoids on neurotransmission and cellular mechanisms of neuroprotection. Furthermore, the paradox of how both CB_1 agonists and antagonists exert similar effects on LID and other hyperkinetic movement disorders

needs to be explained. Future studies should address not only motor and behavioral effects of cannabinoids but, because of their proven effects on the sensory system, also explore their effects on sensory-motor integration, a disorder which is increasingly recognized as an aspect of movement disorders.[114]

Several factors may help explain conflicting preclinical results. Given that cannabinoids interact with a wide range of pharmacological targets, discrepancies in data obtained from preclinical studies may partly reflect the multiplicity of cannabinoid actions.[115] The complex localization of cannabinoid receptors at different sites in basal ganglia circuits and the broad array of formulations and doses used in preclinical and clinical studies may also help explain contradictory results.[8, 50]

A change in classification from Schedule I to Schedule IV or V would not only improve access to medical marijuana but could facilitate development and conduct of clinical trials for cannabinoids.[116] Future clinical trials should be adequately powered, employ appropriate methodology and outcome measures for the specific movement disorder studied and assess blinding adequacy.[117] Improved knowledge of cannabinoids and their pharmacology may help identify specific cannabinoids or combinations that provide therapeutic or neuroprotective benefits in patients with movement disorders.

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Table 1

Summary of compounds mentioned in this review

Compound Classification	Cannabinoid/Cannabinoid Reuptake or Enzyme Inhibitor	Biochemical Action
Phytocannabinoid	Δ9-Tetrahydrocannabinol (THC)	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	Cannabinol (CBN)	cannabinoid receptor type 1 agonist; higher affinity for cannabinoid receptor type 2 agonist
	Cannabidiol (CBD)	Low affinity for cannabinoid receptor type 1 and cannabinoid receptor type 2; cannabinoid receptor type 1 antagonist; cannabinoid receptor type 2 antagonist; inhibition of AEA uptake and metabolism
	Δ9-Tetrahydrocannabivarin (Δ9-THCV)	cannabinoid receptor type 1 antagonist; cannabinoid receptor type 2 antagonist
Synthetic Cannabinoid	CP55,940	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	Nabilone	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	WIN 55,212-2	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	HU-210	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	Δ9-Tetrahydrocannabinol (Dronabinol)	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	Levonantradol (CP50,556-1)	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	Arachidonyl-2′-chloroethylamide (ACEA)	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	HU-308	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	AM251	Selective cannabinoid receptor type 1 antagonist
	CE	Selective cannabinoid receptor type 1 antagonist
	Rimonabant (SR141716A)	Selective cannabinoid receptor type 1 antagonist
	SR144528	Selective cannabinoid receptor type 2 antagonist
	6-Iodopravadoline (AM630)	cannabinoid receptor type 1 antagonist; cannabinoid receptor type 2 weak partial agonist
	HU-211	No cannabinoid action; N-methyl-D-aspartate receptor antagonist.
	Nabiximols (Sativex)	cannabinoid receptor type 1 direct agonist; cannabinoid receptor type 2 direct agonist
Endocannabinoid	Anandamide (AEA)	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
	2-arachidonoylglycerol (2-AG)	cannabinoid receptor type 1 agonist; cannabinoid receptor type 2 agonist
Cannabinoid Reuptake Inhibitor	N-arachidonoylaminophenol (AM404)	anandamide transport inhibitor
	UCM707	anandamide transport inhibitor
	VDM-11	anandamide transport inhibitor
Enzyme Inhibitor	URB597	fatty acid amide hydrolase inhibitor

Table 2

Preclinical Neuroprotective Studies of Cannabinoids

Movement disorder	Model	Results	Reference
Parkinson's disease	Human neuroblastoma cells (SH-SY5Y) exposed to several PD-relevant toxins (MPP, lactacystin and paraquat)	THC was neuroprotective. Neuroprotection was not blocked by CB1 antagonist (AM251). WIN 55, 212-2, nabilone, and CBD were not neuroprotective. Peroxisome-proliferator-activated receptors (PPAR) appears critical to neuroprotective effects.	24
	Neuroblastoma cells	HU-210 (CB1 and CB2 receptor agonist), HU-211 (NMDA antagonist), cannabidiol, or 7-hydroxy- cannabidiol were not neuroprotective.	119
	PC12 dopaminergic neuronal cells with proteasomal synthase inhibitor exposure.	WIN55,212-2 was neuroprotective and countered accumulation of alpha-synuclein and parkin.	120
	Paraquat exposed Drosophila melanogaster	CP55,940 (CB1 and CB2 receptor agonist) increased survival when given prior to paraquat exposure and rescued the motor phenotype after exposure.	22
20	6-hydroxydopamine rats	UCM707 (selective AEA reuptake inhibitor) did not provide neuroprotection. AM404 (AEA reuptake inhibitor with additional antioxidant effects) did provide neuroprotection.	67
	6-hydroxydopamine rats	ACEA (selective CB1 receptor agonist), UCM707 (AEA transport inhibitor), and WIN55,212-2 did not reverse neurodegeneration. HU-308 (selective CB2 receptor agonist) produced slight recovery. AM404 (AEA transport inhibitor with antioxidant properties) and CBD were neuroprotective.	21
	6-hydroxydopamine rats; lipopolysaccharide (LPS) lesioned mice	D9-THCV and CBD are neuroprotective in rats, independent of CB2 receptor function. D9-THCV and HU-308 (selective CB2 agonist) attenuated neurodegeneration in mice model and CB2 receptor deficient mice were mover vulnerable to LPS lesion.	118
	6-hydroxydopamine rats; 6-hydroxydopamine exposed mouse cerebellar granule cells	THC and CBD reduced in vivo neurodegeneration. HU-210 (CB1 and CB2 receptor agonist) increased cell survival, particularly when glia were included in culture.	20
	MPTP knockout mice including CB1 and CB2 receptor knockouts	WIN55,212-2 and JWH015 (CB2 receptor agonist) were neuroprotective. Effects were reversed by JTE907 (CB2 receptor antagonist), unchanged in CB1 knockouts and exacerbated in CB2 knockouts. Effects may be mediated by reduced microglia activation.	121
Huntington's disease	Pheochromocytoma cells expressing mutant huntintgin	HU210 (CB1 and CB2 receptor agonist) had small but significant effect on cell survival including cAMP and extracellular signal-reulated kinase (ERK) mechanisms, but also had potentially toxic downstream effects including increased huntingtin aggregation.	126
	Malonate rats	UCM707 (AEA transport inhibitor) did not provide neuroprotection in malonate animals	67
	Malonate rats	THC and SR141716A (selective CB1 receptor antagonist) exacerbated neurotoxicity.	28
	Malonate rats	THC/CBD compound was neuroprotective. SR141716 (selective CB1 receptor antagonist) and AM630 (selective CB2 receptor antagonist) both attenuated neuroprotective effects.	127
	Quinolinic acid rats	WIN55,212-2 (CB1 and CB2 receptor agonist) exerted neuroprotective effects and reduced extracellular glutamate. AM-251 (CB1 receptor antagonist) reversed WIN55,212-2 effects.	124
	3NP rats	3NP toxicity was associated with CB1 receptor reduction and THC was neuroprotective.	122
	3NP rats	CBD, but not ACEA (CB1 receptor agonist) or HU-308 (selective CB2 receptor agonist), were neuroprotective. Rimonabant (SR141716A; selective CB1 receptor antagonist), capsazepine (TRPV1 antagonist) and MSX-3 (adenosine 2A antagonist) did not reverse effects of CBD.	145

Movement disorder	Model	Results	Reference
	Malonate mice including CB2 receptor knockout	HU-308 (selective CB2 receptor agonist) was neuroprotective and reduced proinflammatory markers (TNF-alpha). Effects were reversed by SR144528 (selective CB2 receptor antagonist). CBD and ACEA (CB1 and CB2 receptor agonist) were not neuroprotective.	125
	Mice expressing human mutant huntingtin or quinolinic acid exposure including CB2 receptor knockout mice	CB2 knockouts had increased microglial activation and reduced lifespan with mutant Huntington and quinolinic acid administration. HU-308 (selective CB2 receptor agonist) reduced quinolinic acid neurotoxicity including reduced microglial activation.	123

Abbreviations: 3NP: 3-Nitropropionic acid, CB1: cannabinoid receptor type 1, CB2: cannabinoid receptor type 2, CBD: cannabidiol, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxin, PD: Parkinson's Disease, THC: Δ9-Tetrahydrocannabinol

Table 3

Preclinical studies assessing therapeutic symptomatic efficacy of cannabinoids for movement disorders

Movement disorder	Model	Outcome	Reference
Parkinson's disease	6-hydroxydopamine lesioned rats	AM404 (AEA transport inhibitor) reduced parkinsonian motor asymmetries possibly mediated through stimulation of 5-HT(1b) receptors.	44
	6-hydroxydopamine lesioned rats	Rimonabant (CB1 receptor antagonist) and AM251 (CB1 receptor antagonist) exert antiparkinsonian effects after very severe (>95%) but not severe (85–94%) nigral degeneration possibly due to antagonistic effects of nigra-mediated activity with partial lesions.	46
	6-hydroxydopamine lesioned rats	D9-THCV (CB1 receptor antagonist in vivo per authors) and rimonobant (CB1 receptor antagonist) improved mobility. CP55,940 (CB1 and CB2 receptor agonist) reduced ambulation. Effects appear to be mediated by increased glutamate and not dopamine.	118
	6-hydroxydopamine lesioned rats	HU-211 (CB1 receptor agonist) improved dopamine induced rotations. HU-211 (NMDA antagonist), cannabidiol and 7-hydroxy-cannabidiol did not improve affect rotations.	119
	6-hydroxydopamine lesioned rat	Rimonabant CB1 receptor antagonist) decreased LID with minimal increase in hypokinesia. Effect increased over time and was associated with relative preservation of dopamine neurons in treated animals.	128
	6-hydroxydopamine lesioned rats	Rimonabant (CB1 receptor antagonist) attenuated hypokinesia in rats without influencing dopamine, GABA or glutamatergic transmission.	49
	6-hydroxydopamine lesioned rats	Acute injections of rimonabant (CB1 receptor antagonist) improved parkinsonism when given without levodopa, improved effect of moderate dose levodopa but did not alter dyskinetic effects of high dose levodopa.	48
	6-hydroxydopamine lesioned rats	WIN55,212-2 (CB1 and CB2 receptor agonist) ameliorated levodopa induced abnormal involuntary movements. The beneficial effects of WIN55,212-2 were reversed by AM251 (selective CB1 receptor antagonist) and with reductions in protein kinase A (PKA) and cAMP-regulated phosphorylation of DARPP-32.	131
	6-hydroxydopamine lesioned rats	WIN 55,212-2 (CB1 and CB2 receptor agonist) ameliorated levodopa induced abnormal involuntary movements (AIMs). URB597 (FAAH inhibitor) amerliorated AIMs only when coadministered with capsazepine (TRPV1 antagonist).	54
	6-hydroxydopamine lesioned rats	Intrpallidal and intrstriatal ifusions of CP55,940 (CB1 and CB2 receptor agonist) induced contralateral rotational behavior which was greater in lesioned than unlesioned rats.	40
	6-hydroxydopamine lesioned rats made dyskinetic with 6 weeks of levodopa injections	Highest dose of HU210 (CB1 and CB2 receptor agonist) reduced some abnormal involuntary movements (AIMs) but also impaired normal motor functioning in dyskinetic animals. AM251 (CB1 antagonist) had no effect on AIMs and rimonabant (CB1 antagonist) induced certain AIMs.	55
	6-hydroxydopamine lesioned mice; reserpine administration to mice	Administration of URB597 (FAAH inhibitor) improved long-term depression in globus pallidus medium spiny neurons and enhanced quinpirole (D2/D3 agonist) effects on hypokinesia but had no effect given in isolation.	42
	MPTP-lesioned rhesus monkeys	CE (selective CB1 receptor antagonist) had did not effect motor behavior but increased responses to low levodopa doses. CE did not affect LID.	53
	MPTP lesioned marmosets	Coadministration of levodopa and nabilone (CB1 and CB2 receptor agonist) reduced on-period dyskinesia without reducing antiparkinsonian effects.	52

Movement disorder	Model	Outcome	Reference
	MPTP lesioned marmosets	URB597 (FAAH inhibitor) reduced levodopa induced hyperactivity but not dyskinesias, antiparkinsonian actions or psychosis. There were no behavioral effects when given without levodopa.	129
	MPTP lesioned cynomolgus monkeys	SR141716A (CB1 receptor antagonist) did not induce behavioral changes in unlesioned animals and did not affect parkinsonism post-MPTP administration. In unlesioned animals, levonantrol (synthetic cannabinoid agonist) reduced general activity levels and produced bradykinesia and THC produced bradykinesia without effecting general activity.	38
	MPTP-lesioned marmosets and cynomolgus monkeys	Rimonabant (CB1 receptor antagonist) improved LID when coadministered with levodopa without affecting antiparkinsonian effects. Reductions in endogenous cannabinoid levels were associated with MPTP-lesion but no association was found with LID.	45
	MPTP treated marmosets	THC improved locomotor activity and hand-eye coordination but was associated with worsening AIMs score.	133
	Reserpine rat	THC had no hypokinetic effect by itself but produced a more than 20-fold increase in the reserpine-induced hypokinesia. This effect was slightly increased by physostigmine (cholinesterase inhibitor), completely blocked by ethopropzaine (anticholinergic) and unaffected by scopolamine or naloxone.	132
	Reserpine Rat	Rimonabant (CB1 receptor antagonist) levodopa induced hyperactivity. WIN55,212-2 (CB1 and CB2 receptor agonist) also reduced levodopa induced hyperactivity and reduced antiparkinsonian benefits when given at highest dose. AM404 (AEA transport inhibitor) had no effect on hyperkinesia.	43
	Anadamide (AEA) treated rats	AEA (CB1 and CB2 receptor agonist) induced hypokinesia. Capsazepine (vanilloid antagonist) reversed effects of AEA. In vitro experiments demonstrate AEA reduces K(+)-stimulated anigrostriatal dopamine release through vanilloid-like receptors.	134
Huntington's Disease	3NP rats	Arvanil (CB1 and TRPV1 receptor agonist) significantly reduced hyperkinetic activity in lesioned animals and increased glutamate in the globus pallidus. It also reduced ambulation and other activity in both lesioned and control animals.	66
	3NP rats	UCM707 (AEA transport inhibitor) reduced hyperkinetic activity and increased both glutamate and GABA levels in the globus pallidus.	67
	3NP rats	AM404 (AEA transport inhibitor) attenuated motor hyperactivity, reduced ambulatory activity and improved toxin-induced GABA and dopamine deficits.	63
	3NP rats	AM404 (AEA transport inhibitor) reduced hyperkinesia and was reversed by capsazepine (VR1 antagonist) but not rimonabant (CB1 antagonist). VDM11 (CB reuptake inhibitor) and AM374 (CB hydrolysis inhibitor) did not reduce chorea. Capsaicin (VR1 agonist) and CP55,940 (CB1 and CB2 receptor agonist) reduced hyperkinesia but only capsaicin improved basal ganglia GABA and dopamine deficits.	146
	R6/1 transgenic mice	HU210 (CB1 and CB2 agonist) and THC did not affect motor deterioration and HU210 treatment was associated with seizures and increased ubiquinated aggregates in the striatum.	135
Tremor	EAE mice	WIN 55,212, THC, and JWH-133 (CB1 and CB2 receptor agonists) and methanandamide, (CB1 agonist) reduced tremor and spasticity. Pretreatment with rimonabant or SR144528 (CB antagonists) eliminated ability of agonists to reduce tremor and CBD had no effect.	92

Movement disorder	Model	Outcome	Reference
	NMDA induced tremor in mice	HU-211 (nonpsychotropic synthetic cannabinoid with NMDA antagonist effects and without CB receptor effects) blocks NMDA-induced tremor.	137
Dystonia	SKF81297 (D1 agonist) or haloperidol (D2 antagonist) treated Cebus apella monkeys	SKF-induced oral dyskinesia was dose dependently reduced by CP55,940 (CB1 and CB2 receptor agonist), with no effect of rimonabant (CB1 antagonist). Haloperidol-induced dystonia was not affected by either CP55,940 or rimonabant.	130
	dt ^{sz} mutant hamsters	Rimonabant (selective CB1 antagonist) did not affect dystonia. WIN55, 212-2 (CB1 and CB2 receptor agonist) exerted antidystonic effects. Cannabidiol delayed the progression of dystonia only at a high dose. The effects of WIN 55,212-2 were antagonized by pretreatment with rimonabant.	75
	dt ^{sz} mutant hamsters	WIN 55,212-2 (CB1 and CB2 receptor agonist) improved dystonia at higher doses but also reduced spontaneous motor activity and induced catalepsy. At lower doses, WIN 55,212-2 had no effect but had therapeutic efficacy when coadministered with a subtherapeutic dose of diazepam.	74

Abbreviations: AEA: anandamide; AIM: Abnormal Involuntary Movements, CB1: cannabinoid receptor type 1, CB2: cannabinoid receptor type 2, EAE: experimental autoimmune encephalomyelitis, LID: levodopa-induced dyskinesia, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxin, PD: Parkinson's Disease, 3NP: 3-Nitropropionic acid

Table 4

Clinical studies of cannabinoids for movement disorders

Movement disorder	Study Design	Sample Size	Intervention	Outcome	Reference
Parkinson's disease	Randomized, double-blind, placebo-controlled crossover.	17	Cannador standardized to 2.5 mg of D9-THC and 1.25 mg of cannabidiol per capsule. 2 treatment phases, each of 4 weeks duration separated by a 2-week washout phase.	No improvement in LID, motor symptoms, quality of life or sleep.	59
	Case series.	5	One gram marijuana (2–9% THC) smoked as a cigarette on morning of testing.	None of the patients experienced relief or demonstrated improvement of tremor following marijuana.	138
	Case series.	22	After baseline assessment, patients were asked to smoke .5 g of cannabis. 30 minutes later the motor and non-motor battery was repeated.	Significant improvement in tremor and bradykinesia.	135
	Randomized, double-blind, placebo-controlled study.	8	Administered 20 mg rimonabant (CB1 antagonist) or placebo for 9 or 16 days and then gave levodopa challenge.	No effect on LID or motor disability in on or off state.	58
	Randomized, double-blind, placebo-controlled, crossover trial.	5	Nabilone or placebo was administered in 2 split doses 12 hours and 1 hour before levodopa challenges 2 weeks apart.	Rush Dyskinesia Disability Score and LID time was significantly reduced with nabilone vs. control.	60
	Cross-sectional survey.	84	PD registered at Prague Movement Disorders Centre were asked to anonymously complete a questionnaire about their possible experience with cannabis.	39 patients described mild or substantial improvement of PD symptoms, including resting tremor and LID.	61
	Open-label pilot study.	6	150 mg cannabidiol tablet was administered; the dose was increased weekly by 150 mg depending on the clinical response for 4 weeks.	Decreased psychotic symptoms.	57
	Open-label pilot study.	4	Patients administered 75–300 mg/day of cannabidiol.	Decreased REM Behavior disorder per patient and spouse report	139
	Randomized, double-blind, placebo-controlled study.	21	Patients randomized to placebo, 75mg/day cannabidiol or 300 mg/day cannabidiol for 6 weeks.	No change in total UPDRS or any subscales. Improvements were reported for total PDQ-39 score in 300 mg/day group.	140
Huntington's disease	Randomized, double-blind, placebo-controlled crossover trial.	15	Cannabidiol (5 mg/kg) or placebo was given twice daily for 6 weeks.	No effect on chorea severity.	56
	Case study.	1	Self-administered smoked cannabis. Then, patient was administered 1 mg nabilone/day.	Reduction of chorea.	71
	Randomized, double-blind, placebo-controlled crossover study.	37	Four assessment visits were made to each patient at their residence at 5-week intervals. Administered nabilone (1 and 2	Improved motor coordination and chorea. Measures: Unified Huntington's Disease Rating Scale (UHDRS): motor scale,	70

Movement disorder	Study Design	Sample Size	Intervention	Outcome	Reference
			mg) versus placebo. For the last 10 days of each drug interval, patients were taking nabilone 1 or 2 mg/day.	chronic anxiety. Blocked patients were taking nabilone 1 or 2 mg/day.	
			mg) versus placebo. For the last 10 days of each drug interval, patients were taking nabilone 1 or 2 mg/day.	assessment. Blocked patients were taking nabilone 1 or 2 mg/day.	
			mg) versus placebo. For the last 10 days of each drug interval, patients were taking nabilone 1 or 2 mg/day.	chronic anxiety. Blocked patients were taking nabilone 1 or 2 mg/day.	
	Case study.	1	Patient was treated once with 1.5 mg nabilone and 3 hours later was given an evaluation.	Increased chorea.	90
Tremor	Uncontrolled, open clinical trial.	8	Patients with multiple sclerosis, seriously disabled with tremor and ataxia, were given oral tetrahydrocannabinol.	Improved tremor in 2 out of 8 patients.	82
	Randomized, double-blind, placebo-controlled, parallel group.	337	Sativex (nabiximols) or placebo was administered daily for 6 weeks. Patients were assessed at weeks 2 and 6.	No improvement in tremor.	93
	Randomized, double-blind, placebo-controlled crossover.	13	Patients were randomly assigned to receive cannador (containing THC) orally either active treatment for the first 2 weeks followed by placebo for the second 2 weeks or vice versa.	No improvement in tremor.	95
	Randomized, double-blind, placebo-controlled crossover.	57	Group A started with drug escalation: 15–30 mg THC (2.5 mg tetrahydrocannabinol and 0.9 mg cannabidiol) by 5 mg per day for 14 days before placebo. Group B started with placebo for 7 days, crossed to the active period (14 days) and a three-day placebo period	No improvement in tremor.	94
Dystonia	Case study.	1	Smoked one ‘joint’ in the morning once a week for three weeks.	Self-reported improvement with dystonia.	96
	Case series.	5	Oral doses of cannabidiol rising from 100 to 600 mg/day over a 6 week period.	Dystonia assessed with a standard dystonia movement scale, ranging from 0 to 120. Dose-related improvement in dystonia. Cannabidiol at doses over 300 mg/day exacerbated the hypokinesia and resting tremor.	77
	Randomized, double-blind, placebo-controlled crossover.	15	A single dose of nabilone or placebo (0.03 mg/kg) was administered.	No significant reduction in dystonia. Measures: dystonia–movement scale portion of the Burke, Fahn, Marsden dystonia scale, adverse effects, and lying and standing blood pressure.	78
	Case study.	1	Smoked cannabis 3–4g/day. Patient was evaluated and reevaluated after 24 hour drug free period.	Significantly improved dystonia. Measures: Burke-Fahn-Marsden dystonia rating scale.	73
	Randomized, double-blind, placebo-controlled study.	7	Dronabinol or placebo was administered daily for 3 weeks.	No improvement in dystonia.	76
Tics	Case study.	1	Within 2 weeks, the daily dose was raised to 15 mg.	Improved tics by 75%. Measures: the Yale Global Tic Severity Scale.	79

Movement disorder	Study Design	Sample Size	Intervention	Outcome	Reference
	Case study.	1	Starting with a morning dose of 5 mg, increased D9-THC during the following 9 weeks.	Improved tic with no adverse effects. Measures: Yale Global Tic Severity Scale, Gilles de la Tourette Syndrome Quality of Life Scale, and the ADHD symptoms, on the Conners' Teacher Rating Scale	81
	Case study.	1	Smoked cannabis (one "cone") per night for 1 year.	Complete remission of tic. Measures: 1 hour examination.	84
	Cross-sectional structured interviews.	17	Prior cannabis use	(82%) experienced a marijuana-induced improvement of their symptoms. Measures: Shapiro Tourette Syndrome Severity Scale	80
	Case study	1	Administered THC once.	Tourette's Syndrome Global Scale, revealed total tic severity score was 41 before treatment and was reduced to 7 just 2 hours after treatment.	86
	Randomized, double-blind, placebo-controlled crossover study.	12	Δ9-THC or placebo was administered once. After a 4 week washout period, patients were crossed over to receive other treatment.	Scores on Global Clinical Impression Scale, Shapiro Tourette-Syndrome Severity Scale, Yale Global Tic Severity Scale, and Tourette-Syndrome Symptom List revealed dose-dependent improvement in tics.	69
	Case study.	1	Combined treatment with risperidone and Δ9-THC	Scores on Global Clinical Impression Scale, Shapiro Tourette-Syndrome Severity Scale, Yale Global Tic Severity Scale, and Tourette-Syndrome Symptom List revealed significant improvement in tics.	87
	Randomized, double-blind, placebo-controlled.	17	During 6 weeks, patients treated with up to 10 mg/day of THC.	Improved tics. Measures: Tourette Syndrome Clinical Global Impressions scale, the Shapiro Tourette-Syndrome Severity Scale, the Yale Global Tic Severity Scale, the self- rated Tourette Syndrome Symptom List, and a videotape-based rating scale.	87
	Case study	3	a. Self-administered smoked cannabis (1–2 cigarettes/day) for four weeks. b. Self-administered smoked cannabis intermittently. 3. Self-administered smoked cannabis (1/2–1 cigarette/day).	Improved tics.	88