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Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders

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Abstract

A complex motor disorder is a combination of various types of abnormal movements that are associated with impaired quality of life (QOL). Current therapeutic options are limited. We studied the efficacy, safety, and tolerability of medical cannabis in children with complex motor disorder. This pilot study was approved by the institutional ethics committee. Two products of cannabidiol (CBD) enriched 5% oil formulation of cannabis were compared: one with 0.25% δ-9-tetrahydrocannabinol (THC) 20:1 group, the other with 0.83% THC 6:1 group. Patients aged 1 to 17 years (n = 25) with complex motor disorder were enrolled. The assigned medication was administered for 5 months. Significant improvement in spasticity and dystonia, sleep difficulties, pain severity, and QOL was observed in the total study cohort, regardless of treatment assignment. Adverse effects were rare and included worsening of seizures in 2 patients, behavioral changes in 2 and somnolence in 1.

Keywords

dystonia, spasticity, movement disorders, cerebral palsy, cannabis, CBD, THC

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Complex motor disorders are a heterogeneous group of neurologic diseases that present with a combination of various types of abnormal movements and postures, including spasticity and dystonia. These abnormal movements and postures are usually associated with serious orthopedic problems, chronic pain, feeding difficulties, constipation, sleep disorder, epilepsy, and impaired quality of life. The etiology of complex motor disorder includes perinatal and postnatal brain injury due to various causes (perinatal hypoxic ischemic injury, stroke, traumatic brain injury, autoimmune diseases, poisoning), and neuro-genetic syndromes. Cerebral palsy is the most common form of childhood-onset complex motor disorder with multiple comorbidities. Prevalence estimates are 2 to 3 per 1000 live births.[1,2]

The goals of complex motor disorder treatment are improvement of quality of life achieved by decreasing abnormal movements and tone; prevention of musculoskeletal complications; pain relief; and resolution of sleep problems. Therapeutic options range from pharmacotherapy to medical and nonmedical invasive procedures, such as botulinum toxin injections, baclofen pump, selective dorsal rhizotomy, and deep brain stimulation.[2] The clinical effects of these therapies are variable and at times poorly sustained. Pharmacologic treatment of these conditions is limited, especially within the pediatric population: some medications may cause serious side effects and some are not approved for children. The mechanism of action of these medications, their dosage and side effects, as well as invasive treatment options have been reviewed by a few authors.[2-7] Cell-based therapy studies have been conducted in small trials using neural progenitor cells, umbilical cord mononuclear cells, and mesenchymal stem cells. Follow-up data have been reported.[8]

Medical cannabis is currently widely used. Cannabinoid-based therapies have been studied for a variety of illnesses, including neurologic diseases, especially drug-resistant epilepsy and movement disorders. The methodology and results of these studies are controversial.[9-20]

Cannabinoid-based medications are phytocannabinoids and synthetic cannabinoids, which have a number of mechanisms of action, including interaction with endocannabinoid receptors.[12] The endocannabinoid system is involved in the

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modulation of many physiological functions, including neurodevelopment, cognition, mood, motor control, feeding behavior, and pain.[15,16] The endocannabinoid system is a complex endogenous signaling system consisting of the 7-transmembrane domain and G protein–coupled receptors, their endogenous ligands, the endocannabinoids, and the enzymes responsible for endocannabinoid biosynthesis and degradation.[21] The most studied endocannabinoid receptors are cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), but endocannabinoids also have other molecular targets. Molecules that are a product of the degrading and biosynthetic pathway of endocannabinoids can interact with other receptors.[21]

Synthetic cannabinoids, such as nabilone, dronabinol, and Sativex, are cannabinoid receptor agonists with effects similar to THC. These have been approved for clinical indications, including spasticity, pain, and intractable epilepsy.[14,16]

Phytocannabinoids are derived from the Cannabis plant (marijuana), which contains more than 80 pharmacologically active cannabinoid compounds.[12,21] The 2 major phytocannabinoids are THC, the main psychoactive constituent of the marijuana plant, and cannabidiol (CBD), a phytocannabinoid that is believed to have no psychoactive properties[22] but more sedating, antiemetic, and analgesic ones.[16] All cannabinoids have the heterocyclic terpeno-phenolic chemical structure and are very lipophilic. They cross the blood-brain barrier, accumulate in lipid-laden tissues, including brain parenchyma and neuronal cell membranes specifically, and are released gradually into the bloodstream over days and weeks.[14,22] The onset of physiological and psychological effects varies depending on the method of treatment administration, with peak effects occurring 30 minutes after inhalation or 1 to 6 hours after ingestion, and lasting for 2 to 4 hours.[12] Cannabinoids are primarily metabolized by the hepatic cytochrome P450 enzyme system.

Acute physiologic effects of cannabis include tachycardia, elevated blood pressure, bronchial relaxation, dry mouth and throat, and conjunctival injection.[12] Psychological effects vary by individual and dose and may be positive (relaxation, euphoria, heightened perception, sociability, sensation of time slowing, increased appetite, and decreased pain) or negative (paranoia, anxiety, irritability, impaired short-term memory, poor attention and judgment, and hindered coordination and balance).[12] Hadland and Harris discussed the physiological and psychological effects of cannabis in chronic users[12] together with changes in cognition, brain structure and brain function, as well as the psychiatric side effects associated with cannabis use.[14]

The therapeutic potential of cannabinoids for movement disorders is based on the current understanding of cannabinoids' pharmacology and mechanism of action.[10,16] CB1 receptors are highly expressed in the central nervous system, especially in the basal ganglia. CB2 receptors are mostly expressed in the immune system, where they modulate inflammation, but they have also been found in the basal ganglia, in neurons within the dorsal vagal motor nucleus, the nucleus ambiguous, the spinal trigeminal nucleus, and microglia.[16]

Animal models suggest that CB1 agonists reduce overactivity of the globus pallidus interna and improve dystonia by reducing γ-aminobutyric acid (GABA) reuptake.[16] THC has been found to bind to CB1 and CB2 receptors. Cannabidiol does not activate CB1 and CB2 receptors, but inhibits endocannabinoid degradation and interacts with many other, non-endocannabinoid-signaling systems.[10] Cannabidiol may also potentiate some of THC's beneficial effects as it reduces the psychoactivity of THC, thus allowing patients to tolerate higher amounts of THC.[10] Cannabidiol may also supplement the antispastic effects of THC (eg, via local potentiation of glycine signaling, inhibition of endocannabinoid degradation, or retardation of demyelination through anti-inflammatory, antioxidant, and antiexcitotoxic mechanisms).[10] Kluger et al have reviewed preclinical and clinical studies regarding the therapeutic potential of cannabinoids for movement disorders.[16] Most of the studies included in the review had been conducted in adults. The efficacy of medical cannabis in pediatric complex motor disorder has not been established yet.

Methods

The present intervention study was approved by the Ethics Committee of the Wolfson Medical Center, Holon. The parents or legal guardian of the patient gave written informed consent before their child was enrolled in the study. The inclusion criteria included children aged 1-18 years, diagnosed with complex motor disorder with predominant dystonia, spasticity, or both; normal electrocardiogram; and a stable medical condition (no cardiorespiratory and renal deterioration). Exclusion criteria were surgical or medical intervention, such as orthopedic surgery or botulinum toxin injections, scheduled during the study period or in the 6 months prior to study entry, and psychiatric illness in a patient or first-degree relative.

Two products of cannabidiol-enriched 5% oil formulation of the cannabis strain Avidekel (Tikun Olam Ltd) were compared: cannabidiol-to-THC ratio 6:1 and cannabidiol-to-THC ratio 20:1. The aim was to check the difference in efficacy between cannabidiol and THC on spasticity, dystonia, sleep, mood, constipation, and appetite. One group of patients received cannabidiol to THC in a ratio of 20:1 (ie, a minimal amount of THC) and the other group received cannabidiol to THC in a ratio of 6:1 (ie, a higher amount of THC).

The analysis and quality assurance followed the high standards of ISO-9001, HACCP–Hazard Analysis, GAP–Good Agricultural Practice, Pesticides & microbiology Control (Tikun Olam Ltd).

Two types of medication were randomly selected. The initial dose was 1 drop 3 times daily (cannabidiol 6 mg and THC 0.99 mg for the 6:1 group and cannabidiol 6 mg and THC 0.3 mg daily for the 20:1 group). The dose was up-titrated gradually at different rates until one of the following was observed: intolerance, serious side effects, maximum THC dose of 15 mg per day, or the end of the study. The medication was administered either orally or by feeding tube 2 to 3 times daily for 5 months. Treatment was started after 2 months of observation at the second visit in order to exclude changes due to disease evolution. All other medications, including antiepileptic drugs and medication for dystonia and spasticity, were continued. To prevent side effects due to the combination of benzodiazepines and medical cannabis, clonazepam was reduced in 5 patients, but was restarted in 3 of them because of severe withdrawal symptoms.

Assessments were performed at baseline and at every monthly visit thereafter. Baseline data collected for each participant included a medical and neurologic history, electroencephalogram (EEG), and blood tests: complete blood count, biochemistry tests, liver function tests, creatinine phosphokinase (CPK). During each visit, the patient was examined by a pediatric neurologist and a physical therapist trained in pediatric movement disorders. Each patient was assessed by the Berry Albright Dystonia scale,[23] Gross Motor Function Measure,[24,25] parents' numeric rating scale (NRS)[26] for spasticity, dystonia, estimation of mood, sleep, appetite, and constipation, visual analog scale (VAS) for pain, Cerebral Palsy Child (CPCHILD) questionnaire[27] (chapter 6), and questionnaires for adverse effects. Electrocardiogram (ECG), EEG, and blood tests were repeated for each patient at baseline and at the end of the study. The neurologist was available 24 hours a day in order to manage any side effects of the medication.

Statistical Analysis

Data were recorded on paper forms and uploaded to Excel spreadsheet. Data analyses were conducted using SPSS version 22 for Windows. As this was a pilot study, a power calculation was not performed. Within the scope of the study, it was estimated that it was feasible to recruit 25 participants into the trial. Continuous data are summarized as mean ± standard deviation values with corresponding 95% confidence intervals. Continuous variables were compared by group using the *t* test or Mann-Whitney *U* as appropriate. Within-group before vs after comparisons were made using the paired *t* test or the Wilcoxon signed ranks test as appropriate. Nominal variables are presented as frequency counts and were compared by group using the chi-square test. All tests were 2-sided and considered significant at $P < .05$.

Results

Twenty-five patients were recruited. A total of 20 patients completed the 5-month study. Five patients were withdrawn by their parents because of various causes. One patient from the 6:1 group developed severe irritability and inappropriate crying and laughing under 60 mg of cannabidiol/10 mg of THC; the titration was 3 drops weekly. Two patients showed lack of improvement after a 2-month treatment period. One patient demonstrated worsening of seizures, and 1 patient did not start the treatment because of emergency orthopedic surgery between visits 1 and 2. These patients were analyzed as intention to treat.

Details of the participants are shown in Tables 1 and 2. The mean age was 6.51 years (range 1-16.8 years), with 16 males and 9 females. Nineteen patients were diagnosed with cerebral palsy, 5 patients had a neurogenetic syndrome and 1 child had complex motor disorder due to traumatic brain injury. The Gross Motor Function Classification System (GMFCS) score was 5 in 17 patients (68%), 4 in 7 (28%), and 3 in 1 (4%). Six patients had epilepsy or a history of seizures prior to the study. An abnormal electroencephalogram was found in 7 patients, and all were treated with antiepileptic medications, including phenobarbital, clonazepam, lamotrigine, topiramate, and valproic acid. Four patients were treated with trihexyphenidyl, 5 with baclofen, 1 with tetrabenazine, and 1 had a baclofen pump. The medication was administered by feeding tube in 6 patients. The maximal dose of cannabidiol and THC was 90 mg/d and 14.85 mg/d relatively in the 6:1 group and 210 mg/d and 10.50 mg/d in the 20:1 group (shown in Table 1).

Table 1. Baseline characteristics of the Study Population.

Measure	6:1 group	20:1 group	*P* value
Age, y	7.15 ± 4.63	5.71 ± 4.97	.46
Mean THC, mg/d (visit 7)	6.27 ± 7.20	3.67 ± 3.61	.32
Mean CBD, mg/d (visit 7)	38 ± 43.67	91.75 ± 69.11	.06
Mean THC, mg/kg/d (visit 7)	0.61 ± 0.69	0.28 ± 0.24	.22
Mean CBD, mg/kg/d (visit 7)	3.73 ± 4.18	5.53 ± 4.85	.42
Absolute THC, mg/d	14.85	10.50	
Absolute CBD, mg/d	90	210	
Maximal THC, mg/kg/d	1.78	0.76	
Maximal CBD, mg/kg/d	10.79	15.22	
Female sex, %	35.7	36.4	.97
Diagnosis, %, CP/G	71.4/28.6	81.8/18.2	.55
GMFCS, %			.51
3	7.10	0.00	
4	21.40	36.40	
5	71.40	63.60	
FT, %	21.4	27.3	.73

Abbreviations: CBD, cannabidiol; CP, cerebral palsy; FT, feeding tube; G, neurogenetic syndrome; GMFCS, Gross Motor Function Classification System; THC, δ-9-tetrahydrocannabinol.

Table 3 presents Berry Albright Dystonia scale; Gross Motor Function Measure; Cerebral Palsy Child questionnaire; numeric rating scale for spasticity, mood, appetite, stool function, and sleep; and visual analog scale scores by visit. Except for numeric rating scale for dystonia, changes in scores were not observed between visit 1 and visit 2. Numeric rating scale for spasticity, Gross Motor Function Measure overall and Dimension A (laying and rolling) and Dimension B (sitting) improved from baseline in the entire study population regardless of treatment assignment. The cohortwide improvement in dimension A appears to be attributable to the improvement in the 6:1 group.

The Cerebral Palsy Child questionnaire for quality of life (QOL) improved in the total study cohort. Additionally, numeric rating scale for mood, stool function, sleep, and appetite statistically improved in the whole group. The overall improvement in constipation appears to be driven by the improvement in the 20:1 group, whereas the overall change in sleep is driven by the improvement in the 6:1 group. Visual analog scale scores improved significantly in the whole group as did pain duration and frequency.

Dystonia and QOL improved in the 20:1 group under a mean dosage of THC 3.67 ± 3.61 mg/d, 0.28 ± 0.24 mg/kg/d, and cannabidiol 91.75 ± 69.11 mg/d, 5.53 ± 4.85 mg/kg/d. In contrast, in the 6:1 group, QOL improved under a mean dosage of THC 6.27 ± 7.20 mg/d, 0.61 ± 0.69 mg/kg/d, and cannabidiol 38 ± 43.67 mg/d, 3.73 ± 4.18 mg/kg/d.

Table 2. Characteristics of the Study Population.

Patients	CPK, start	CPK, end	Medications at the start	Medications at the end	EEG, start	EEG, end	Seizure
6:1 group							
1	NA	117 (20-117)	Clonazepam	Clonazepam	EA	NA	History
2	NA	NA	No	No	N	NA	No
3	NA	NA	Neuleptil	Neuleptil	N	NA	No
4	NA	NA	No	No	N	N	No
5	NA	470	No	No	N	N	No
6	NA	NA	No	No	N	NA	No
7	213 (20-200)	233 (20-200)	Baclofen, clonazepam, trihexyphenidyl	Baclofen, clonazepam, trihexyphenidyl	EA	EA	No
8	NA	NA	Valproic acid	Valproic acid	EA	NA	Current
9	NA	NA	Clonazepam	No	NA	NA	No
10	122 (0-150)	146 (0-150)	Topiramate, lamotrigine	Topiramate, lamotrigine	EA	EA	Current
11	NA	NA	Trihexyphenidyl, baclofen pump	Trihexyphenidyl, baclofen pump	NA	NA	No
12	NA	NA	Adderall, clonidine, melatonin, colchicine	Adderall, clonidine, melatonin, colchicine	NA	NA	No
13	N	NA	Clonazepam, Baclofen, dantrolene, trihexyphenidyl	Clonazepam, baclofen, dantrolene, trihexyphenidyl	N	NA	History
14	NA	N	Clonazepam, baclofen, lamotrigine, Nozinan, omeprazole	Clonazepam, baclofen, lamotrigine, Nozinan, omeprazole	N	N	Current
20:1 group							
15	351 (0-160)	NA	Trihexyphenidyl	Clonazepam, risperidone	NA	NA	No
16	157 (0-157)	NA	Baclofen, clonazepam	Clonazepam	N	NA	No
17	NA	NA	Clonazepam, trihexyphenidyl, tetrabenazine, Scopoderm patch	Clonazepam, trihexyphenidyl, tetrabenazine, Scopoderm patch	NA	NA	No
18	177 (160)	NA	Clonazepam	Trihexyphenidyl	EA	NA	No
19	104	170 (0-145)	Clonazepam, fluoxetine	Clonazepam, fluoxetine	N	NA	No
20	N	NA	Clonazepam	No	NA	NA	No
21	NA	NA	Phenobarbital	Phenobarbital	EA	NA	No
22	N	NA	Levetiracetam, clonazepam	Levetiracetam, valproic acid, clonazepam	EA	EA	Current
23	180 (0-150)	159 (0-150)	Clonazepam	No	N	NA	No
24	NA	NA	Phenobarbital, omeprazole	Phenobarbital, omeprazole	N	NA	Current
25	N	N	No	No	N	N	No

Abbreviations: THC, δ-9-tetrahydrocannabinol; CBD, cannabidiol; EA, epileptic activity; N, normal; NA, not available.

A total of 15 patients continued medical cannabis therapy. All available EEGs indicated neither benefit nor worsening. There were no changes in ECG or blood tests. Of the 4 patients with elevated CPK before the onset of treatment and available CPK titers, 1 patient's CPK level decreased and the 3 others increased by the end of the study (Table 2). Abnormalities of hepatic aminotransferase levels were found in 1 patient, before the study. There was no worsening during the study period. Reported side effects included a worsening of seizures in 2 patients who had partially controlled seizures before the intervention. This was not accompanied by a worsening of epileptic activity on EEG. Two patients, 1 from each group, developed behavioral changes: the first child from the 6:1 group manifested excitation due to rapid titration of the medication, with complete normalization after tapering. The second patient developed mood fluctuations under a combination of a morning dose of Ritalin LA 20 mg and cannabidiol-THC 20:1. Termination of methylphenidate was effective in controlling the behavioral changes. Additionally, 1 patient from the 6:1 group developed somnolence at a cannabidiol dose of 18 mg/d (1.8 mg/kg/d) and THC dose of 2.97 mg/d (0.3 mg/kg/d). Dose reduction improved the patient's alertness, and the patient was maintained on the lower dose.

Discussion

There are only 2 studies regarding the efficacy and safety of cannabinoids in pediatric movement disorders. In 2004 Lorenz demonstrated the efficacy of dronabinol (synthetic pure δ-9-tetrahydrocannabinol [THC] in an oil-filled soft gelatin capsule) in 8 patients with neurologic diseases of different etiology (neurodegenerative, mitochondrial diseases, post-hypoxic state, epilepsy, posttraumatic reaction).[9] He reported that dronabinol reduced spasticity and dystonia, increased patient interest in his/her surroundings, and had an anticonvulsive effect.

Kuhlen et al reported positive effects of dronabinol in 16 patients, aged 1.3-26.6 years, in specialized pediatric palliative care, with complex neurologic conditions and resistant

Table 3. Outcome Measures Scores.[a]

	Visit 1	Visit 2	Visit 4	Visit 7	*P* value
All patients					
BADS	15.68 ± 6.23	15.52 ± 5.92	14.90 ± 5.66	12.69 ± 4.62	.009
NRS for dystonia	7.36 ± 2.63	8.32 ± 1.35	6.83 ± 2.40	6.40 ± 2.68	.002
NRS for spasticity	8.29 ± 1.16	8.08 ± 1.55	6.83 ± 2.35	6.60 ± 2.43	.002
GMFM total	11.49 ± 16.20	12.16 ± 15.39	11.16 ± 10.23	14.71 ± 15.06	.001
GMFM lay	34.82 ± 3.42	36.63 ± 29.63	38.40 ± 28.44	44.39 ± 29.88	.001
GMFM sit	13.13 ± 21.44	15.60 ± 22.21	14.10 ± 17.32	19.72 ± 23.27	.009
QOL	40 (0-80)	40 (0-80)	60 (20-80)	60 (20-80)	.036
VAS	5.68 ± 3.14	5.98 ± 2.88	4.70 ± 3.09	4.27 ± 2.65	.022
Mood	4.56 ± 1.64	4.68 ± 1.65	4.96 ± 1.57	5.32 ± 1.35	.018
Appetite	5.00 ± 1.67	4.68 ± 2.00	5.00 ± 1.91	5.32 ± 1.80	.027
Stool	4.44 ± 2.02	4.60 ± 1.98	5.04 ± 2.01	5.74 ± 1.69	.021
Sleep	3.48 ± 2.00	3.80 ± 1.80	4.54 ± 1.56	5.08 ± 1.19	.002
6:1 group					
BADS	14.64 ± 7.58	14.93 ± 6.56	13.97 ± 6.89	11.97 ± 5.39	.951
Dystonia NRS	6.64 ± 3.18	7.86 ± 1.23	6.33 ± 2.64	6.57 ± 2.17	.087
NRS spasticity	8.21 ± 1.18	7.86 ± 1.56	6.62 ± 2.06	6.93 ± 1.86	.011
GMFM total	12.57 ± 20.38	12.91 ± 19.21	10.16 ± 10.08	15.33 ± 17.69	.284
GMFM lay	32.92 ± 21.8	34.18 ± 31.5	34.54 ± 27.67	41.87 ± 31.50	.047
GMFM sit	14.88 ± 26.05	16.67 ± 26.47	12.18 ± 15.59	22.42 ± 27.07	.695
QOL	46.67 ± 21.46	43.08 ± 21.36	60.00 ± 19.07	55.38 ± 20.56	.011
VAS	6.22 ± 2.87	6.24 ± 3.18	4.78 ± 3.36	4.74 ± 2.63	.426
Mood	4.43 ± 1.60	4.36 ± 1.44	4.92 ± 1.61	5.29 ± 1.50	.057
Appetite	4.82 ± 1.83	4.72 ± 1.85	5.30 ± 1.57	5.36 ± 1.57	.098
Stool	5.42 ± 1.87	5.14 ± 1.79	5.38 ± 2.02	5.69 ± 1.80	.751
Sleep	3.43 ± 1.87	3.71 ± 1.73	5.08 ± 0.95	5.36 ± 0.63	.011
20:1 group					
BADS	17.00 ± 3.87	16.27 ± 5.13	16.00 ± 3.80	13.55 ± 3.56	.021
Dystonia NRS	8.27 ± 1.35	8.91 ± 1.30	7.36 ± 2.11	6.18 ± 3.31	.036
NRS spasticity	8.40 ± 1.17	8.36 ± 1.57	7.09 ± 2.74	6.18 ± 2.06	.048
GMFM total	10.12 ± 9.28	11.21 ± 9.29	12.33 ± 10.76	13.93 ± 11.69	.054
GMFM lay	37.25 ± 29.91	39.75 ± 28.25	42.96 ± 29.99	47.59 ± 28.85	.079
GMFM sit	11.36 ± 14.60	14.24 ± 16.44	16.36 ± 19.69	16.51 ± 18.60	.277
QOL	30.91 ± 20.71	34.55 ± 28.41	49.09 ± 16.40	57.78 ± 12.02	.023
VAS	4.91 ± 3.49	5.61 ± 2.52	4.58 ± 2.89	3.62 ± 2.67	1
Mood	4.73 ± 1.74	5.09 ± 1.87	5.00 ± 1.61	5.36 ± 1.21	.185
Appetite	5.25 ± 1.49	4.63 ± 2.33	4.63 ± 2.33	5.25 ± 2.19	.891
Stool	3.18 ± 1.47	3.91 ± 2.07	4.64 ± 2.01	5.80 ± 1.62	.011
Sleep	3.55 ± 2.25	2.91 ± 1.92	3.91 ± 1.92	4.73 ± 1.62	.107

Abbreviations: BADS, Barry Albright Dystonia Scale; GMFM, Gross Motor Function Measure; NRS, numeric rating scale; QOL, quality of life; VAS, visual analog scale.

[a]Results for all measurements are presented as mean ± SD.

spasticity.[15] The dosages necessary to achieve a therapeutic effect varied from 0.08 to 1.0 mg/kg/d with a median of 0.33 mg/kg/d. Side effects were rare and consisted only of vomiting and restlessness. Though the study was prospective and side effects were closely monitored, the efficacy of dronabinol was assessed by the parents, nurses, and physiotherapists, without standardized testing.

Our pilot study indicates that cannabidiol-enriched 5% oil formulation of cannabis with ratios of cannabidiol to THC of 6:1 and 20:1 is effective in children with complex motor disorder by reducing the severity of dystonia and spasticity, and improving motor function ability and quality of life. All participants demonstrated mood and appetite improvement, patients who received a product with cannabidiol-to-THC ratio of 20:1 demonstrated improved constipation, whereas subjects treated with higher amount of THC (cannabidiol-to-THC ratio of 6:1) demonstrated sleep improvement.

We did not find a difference between the 2 medications in the antispastic effect. Spasticity reduction in our patients was achieved by a median dosage of THC of 0.44 mg/kg/d compared to 0.33 mg/kg/d in the Kuhlen et al study.

Our findings demonstrate that medical cannabis can be administered over at least a 5-month period without severe side effects or aggravating existing symptoms. The worsening of seizures in 1 patient may be related to the reduction of the dose of clonazepam, or to the natural history of the disease. We did not find any interaction of cannabis with the underlying medications, including clonazepam. We observed mood changes in

1 patient treated with methylphenidate. Mood deterioration has not been previously reported in patients treated with a combination of THC and methylphenidate.[28]

Limitations of our study include the small sample size, which makes rejection of the null hypotheses difficult. Additionally, titration of the medication was slow, so that the total time on the optimal dose was limited. This may lead to an underestimation of treatment efficacy. Most importantly, there was no concurrent control group, making it impossible to rule out time as a cause of symptom improvement. Moreover, the placebo effect is a well-known phenomenon in pharmacologic treatment including cannabis[15,29] and could not be excluded in our patients. Lack of verbal contact with most of our patients made the assessment of cognitive impact and psychological side effects difficult. It remains questionable whether tolerance would have developed in these patients. On the other hand, overall improvement in several outcome measures was observed despite the small sample size in the total study cohort. Additional studies using concurrent, non-cannabis-treated controls are needed to more comprehensively assess the efficacy of medical cannabis in children with complex motor disorder.

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Author Contributions

SL made a substantial contribution to the design of the work, as well as acquisition, analysis and interpretation of data. Drafted the article. Approved the version to be published. LBLS made a substantial contribution to the concept and design of the work. NS, LL, YT and IL made a substantial contribution to the acquisition of data. TLS revised the article critically for important intellectual content. LB made a substantial contribution to the concept and design of the work; acquisition, analysis and interpretation of data. Drafted the article and approved the version to be published.

Declaration of Conflicting Interests

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Ethical Approval

The study was conducted in accordance with all ICH-GCP guidelines 0101-14 womc.

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