Review Article

A critical narrative review of medical cannabis in pediatrics beyond epilepsy, part II: neurodevelopmental, movement, and pain disorders

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Background and Objective: Medical cannabis, which exerts its pharmacologic activity through the endocannabinoid system (ECS), has recently been used in children to treat certain diseases beyond epilepsy. This second section of a three-part series contains a comprehensive review of the evidence-based treatment for neurodevelopmental disorders, movement disorders, and pain disorders.

Methods: In this comprehensive review, PubMed, Embase, and Clinicaltrials.gov (1966–May 2020) searches were performed using the key search terms cannabis, neurodevelopmental disorders, child and adolescent psychiatry, spasticity, movement disorders, and pain. Only articles pertaining to cannabis and the pertinent disease states were extracted. Current published literature on the relevant disease states were largely limited to small pediatric trials and case studies.

Key Content and Findings: For diseases with limited pharmacologic treatment or clinical response, including Tourette syndrome (TS), refractory spasticity and epidermolysis bullosa (EB), the medicinal use of cannabis may be considered. The use of high CBD:THC ratios for the management of autism spectrum disorder (ASD) irritability appears promising. The formulations and doses evaluated in the studies commonly had increasing dose titration and varied by disease state.

Conclusions: Further clinical investigations in pediatrics using robust clinical trial designs are necessary to elucidate the role of cannabis, including optimal dosing, formulation and duration of use, to ensure safety and efficacy.

Keywords: Cannabis; medical marijuana; cannabinoids; pediatrics

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Introduction

In the past few decades, a rapid rise has been observed in the awareness and acceptance of cannabis for medical and recreational use, partly due to its legalization in many states in the USA. Coupled to this legalization, the broadening scope of research, and changes to the 2018 Farm Bill, which removed hemp [a cannabis plant with less than 0.3% delta-9-tetrahydrocannabinol (THC)]

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from the Controlled Substances Act, also contributed to the escalating use of cannabis. Irrespective of the legal status over time, it is clear that millions of people globally use cannabis for a myriad of medical conditions. As research continues to advance, it becomes evident that cannabis has a therapeutic role in many disease states, particularly chronic pain, adjunctive cancer treatment, and epilepsy. However, a growing number of healthcare practitioners, including pediatricians, are recommending cannabis for other medical conditions. Furthermore, adults, young adults and parents of pediatric patients are self-initiating treatment without their practitioner's knowledge.

With the abundant literature evaluating the use of cannabis for epilepsy, this three-part series details the uses beyond epilepsy of cannabis and cannabis-derived products for medical conditions reported in the pediatric population. Currently, evidenced-based data are limited for the medical use of cannabis for conditions beyond epilepsy due to small studies, a lack of standardized cannabis formulations, variability in dosing, and inconsistent methodology. Moreover, much of the available research has been conducted on adults, underscoring the need for pediatricians to extrapolate data and independently evaluate the risks and benefits of use in childhood and adolescence.

This is the second article in our three-part series and will focus on the use of cannabis in neurodevelopmental disorders, movement disorders, and epidermolysis bullosa (EB). The purpose of this series is to provide a critical review of the medicinal properties of cannabis to support pediatric healthcare practitioners in making informed and evidence-based decisions for use in their patients.

Methods

This narrative review was conducted by all authors for the purpose of reviewing the available literature on the use of medical cannabis in pediatric disease states. Due to the robust published studies on the use of cannabinoids for epilepsy, the decision was made to narrow our review to other disease states in which cannabis use was not readily known or studied, in order to illuminate providers regarding potential use for other conditions. Our initial search was wide and endeavored to capture any disease state, other than epilepsy, in which any formulation of cannabis was used in the pediatric population. Our search was then narrowed to the following broad medical conditions: autism, behavioral disorders, oncology, autoimmune diseases, spasticity and pain, and genetic and inherited diseases. Based on the limited search results, we organized our findings to report on studies of (I) neurodevelopmental disorders that included autism spectrum disorder (ASD), Tourette syndrome (TS), spasticity, complex motor disorders, and movement disorders; (II) the congenital skin disorder epidermolysis bullosa (EB); and (III) gastrointestinal disorders that included chemotherapy-induced nausea and vomiting (CINV) and inflammatory bowel disease (IBD). We report our findings regarding cannabis use in gastrointestinal disorders in the third part of this three-part series.

Eligibility

The inclusion criteria were only limited to research conducted on the human, pediatric, adolescent and young adult population in the English language. Due to the paucity of search results, there were no limitations on the type of study included.

Information sources

A search in PubMed, Embase, and clinicaltrials.gov up to May 2020 was performed. Our search was conducted using MeSH terms describing cannabis and the particular disease states identified above, for example, "cannabis OR cannabinoid OR medical marijuana AND autism OR spasticity". Sources also included websites from relevant regulatory and professional bodies, such as the American Academy of Pediatrics.

Neurodevelopmental disorders

The cannabis plant exerts its pharmacologic effect through the endocannabinoid system (ECS). Recently, the ECS has been a target of interest for the treatment of psychiatric disorders due to its modulatory effects on learning and memory, emotion, anxiety, and social functioning. Medical cannabis for psychiatric disorders is an emerging field, with a few adult trials demonstrating potentially beneficial effects for the treatment of social anxiety, post-traumatic stress disorder (PTSD), schizophrenia, and attention-deficit/hyperactivity disorder (ADHD) (1). In the pediatric population, there has been a keen focus on the role of the ECS in

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Table 1 Neuropsychiatric studies of cannabis for severe behavioral problems in pediatrics

Author(s)	N	Population	Age	Study design	Product	Dosing (mg/kg/day)[‡]	Symptom assessment	Outcomes[§]
Kruger & Christophersen [2006] (11)	10	ID + SBP	CH, AD	Open-label case series	Dronabinol	0.258	Caregiver report	SIB (70%)
Kurz & Blaas [2010] (12)	1	ASD + SBP	CH	Case report	Dronabinol	3.62 mg daily dose	ABC	Irritability, lethargy, stereotype, hyperactivity, inappropriate speech
Fleury-Teixeira *et al.* [2019] (13)	18	ASD + comorbidities	CH, AD	Observational Study	CBD:THC, 75:1	4.60:0.06	Standardized form	SBP (20%), sleep disorder (75%), ADHD (60%), communication (47%)[¶]
Barchel *et al.* [2019] (14)	53	ASD + comorbidities	CH, AD, LA	Open-label	CBD:THC, 20:1	16:0.8 (initial dose)	Telephone interview	SBP (68%), hyperactivity (68%), sleep problems (71%), anxiety (47%)
Aran *et al.* [2019] (15)	60	ASD + SBP	CH, AD	Retrospective open-label	CBD:THC, 20:1	3.80:0.29	CGIC & HSQ-ASD	SBP (61%), communication (47%), anxiety (39%)
Bar-Lev Schleider *et al.* [2019] (16)	188	ASD	CH, AD	Prospective open-label	CBD:THC, 20:1	79.5:4.0 mg tid (±61.5:3.0 SD)	Standardized form	SBP (61%), communication (47%), anxiety (39%)
Koren *et al.* [2020] (17)	5	FASD + SBP	CH, LA	Open-label case series	'Oral cannabis'[†]	Varied	NCBRF	SBP

[†], children received CBD:THC oil while late adolescent patients inhaled cannabis. [‡], average dose in mg/kg/day unless otherwise specified. [§], percentage of the population with the corresponding symptoms that reported a significant improvement. [¶], calculated as the percentage of patients that experienced an improvement of 30% or more in the corresponding symptom category. ABC, aberrant behavior checklist; AD, adolescent; CH, child; CSGIC, caregiver global impression of change; FASD, fetal alcohol spectrum disorder; HSQ-ASD, home situations questionnaire; ID, intellectual disability; LA, late adolescent; NCBRF, Nisonger child behavior rating form; SBP, severe behavioral problems; SIB, self-injurious behavior.

neurodevelopmental disorders such as autism spectrum disorder (ASD), fetal alcohol spectrum disorder (FASD), ADHD, and children with intellectual disabilities (ID).

Evidence suggests that the dynamic relationship between the ECS and behavior is likely associated with the imbalance of pro- and anti-inflammatory mediators. In particular, it is hypothesized that molecular markers for ASD are related to alterations of enzymatic processes in the formation of the fatty-acid precursors to anandamide (AEA) and 2-Arachidonoylglycerol (2), leading to decreased circulation of these endocannabinoids and AEA signaling disruption (3-5). Decreased AEA signaling has also been shown to be a result of decreased oxytocin levels; deficits in the brain's reward circuitry could contribute to the social impairment associated with ASD (6). In addition, the CB_2 receptors involved in immune function are postulated to exhibit a compensatory increase in expression due to the hypothesized inflammatory nature of this condition (7). In contrast, upregulation of AEA and CB_1 signaling and the relationship with the dopaminergic and glutamatergic neurotransmitter systems seem to be key factors impacting behavior in patients with ADHD and FASD (8,9). The literature suggests that cannabinoids mechanistically may have benefits; however, the adverse effects of impaired thinking, problem solving, learning and memory, respiratory complications (if smoked), and impaired physical coordination may outweigh the benefits for many young children (10).

Severe behavioral problems are the subject of many published and ongoing clinical trials investigating the use of cannabis for symptom management in psychiatric disorders (*Table 1*). Disruptive and aggressive behaviors are common in FASD (18), ASD (19), and ID. Typical behaviors in ASD include stereotypy, irritability, aggression, tantrums, and self-injurious behavior (SIB). Specifically, in FASD and ADHD, disruptive behaviors manifest as hyperactivity, impulsivity, and emotional outbursts. Given the overwhelming comorbidity existing in these disorders (*Table 2*), symptom management with pharmacologic agents is frequently overlapping and difficult to distinguish between each condition.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://

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Table 2 Comparison of clinical manifestations (18,20-27)

Variables	Autism spectrum disorder (ASD)	Fetal alcohol spectrum disorder (FASD)	Attention-deficit/hyperactivity disorder (ADHD)	Intellectual disabilities (ID)
Disruptive behaviors	Aggression	Aggression	Aggression	Aggression
	Self-injurious behaviors	Hyperactivity	Hyperactivity	Self-injurious behaviors
	Frequent tantrums	Impulsivity	Impulsivity	Stereotypic behaviors
	Ritualistic behaviors	Rule-breaking behavior/delinquency		Stimulating movement
	Stereotypic behaviors such as flapping hands, rocking body or spinning in circles			
	Unusual reactions to sounds, smell, taste, look or feel			
	Resistance to change			
	Obsessive interests			
Neurocognitive deficits	Language & social cognition	Language and social cognition	Language and social cognition	Language and social cognition
	-Speech and language delays	-Speech and language delays	-Difficult peer relationships	-Language delay
	-Repetition of phrases or words (echolalia)	-Social communication and interaction problems		-Social skill deficits
	-Giving unrelated answers to questions			-Immature behavior/play
	-Social skills deficits	Learning and memory	Learning and memory	Learning and memory
	-Avoid eye contact	-Learning impairment	-Forgetfulness in routine activities	-Learning disabilities
	-Difficulty understanding others or own feelings	-Poor memory	-High comorbidity with learning disorders	
		-Difficulty with math		
		-Low IQ		
		Executive functioning	Executive functioning	Executive functioning
		-Mood/behavioral self-regulation problems	-Inattention—seems not to listen; difficulty maintaining play, school or home activities	-Immature activities of daily living (self-help skills)
		-Poor reasoning and judgment skills	-Difficulty organizing tasks activities or belonging	
		-Difficulty with attention	-Avoid tasks that require mental effort	
			-Fail to follow-through, careless mistakes, failure to pay attention to details; loses objects	
			-Easily distracted by irrelevant stimuli	

Table 2 (*continued*)

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Table 2 (*continued*)

Variables	Autism spectrum disorder (ASD)	Fetal alcohol spectrum disorder (FASD)	Attention-deficit/hyperactivity disorder (ADHD)	Intellectual disabilities (ID)
Common co-morbidities	Social anxiety disorder	Conduct disorder	Behavior or conduct problems	Anxiety
	ADHD	Language disorders	Anxiety	Depression
	Oppositional defiant disorder	Other medical issues:	Depression	PTSD
	Other medical issues:	-Low birth weight	ASD	Feeding/eating disorders
	-Gastrointestinal problems	-Poor sleep and sucking issues as infant	Tics and Tourette syndrome	Other medical issues:
	-Seizures	-Visual and hearing issues	Learning disorders	-Cerebral palsy
	-Sleep disorders	-Heart, kidney or bone issues	Increased risk of injuries	-Congenital heart disease
		-Shorter height		-Constipation
		-Small head circumference		-Dental caries
		-Poor coordination		-Endocrine disorders
		-Abnormal facial features, such as a smooth ridge between the nose and upper lip (this ridge is called the philtrum)		-Gastroesophageal reflux disease
				-Obesity
				-Seizures
				-Sleep disorders
				-Visual impairment
				-Undescended testes

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pm.amegroups.com/article/view/10.21037/pm-20-69/rc).

Limitation of traditional pharmacotherapy

While pharmacotherapies are available for the treatment of neurodevelopmental disorders, most are prescribed off-label with other limitations to their clinical use. Risperidone and aripiprazole have been shown to be effective for disruptive behaviors associated with ASD (28), FASD (29) and ID (30). These two agents are the only medications approved by the FDA for the use in patients with ASD, specifically labeled for the treatment of irritability (31,32); however, they are also widely used off-label for behavioral symptoms associated with FASD and ID. In addition to atypical antipsychotics, a host of other drug classes are prescribed off-label for severe behaviors problems including mood stabilizers, psychostimulants, and selective serotonin receptor inhibitors. In spite of these options, it is speculated that close to 40% of ASD patients seeking treatment for severe behavior problems develop drug-refractory aggression, SIB, and severe tantrums; in addition, the presence of ID was a predictor of these drug-refractory symptoms (33). There are several agents, including oxytocin nasal spray, in trial to treat the core symptoms of ASD (34). Balovaptan, a vasopressin 1a (V1a) receptor antagonist, is another investigational agent to treat the core symptoms (35). Vasopressin is similar in structure to oxytocin and has a role in promoting social bonding. Vasopressin may be effective in emotional processing deficits and social impairment among those with autism (36).

ASD and ID

The use of cannabis to manage the symptoms of these neuropsychiatric conditions was first reported with dronabinol to treat SIB in children specifically with ID and ASD. In an open-label case series, 7 out of 10 treatment-resistant children and adolescents with ID reported significant improvements in SIB after receiving oral dronabinol doses of 2.5 mg twice daily to 5 mg four times daily (11) (*Table 1*). In another case study investigating dronabinol, a child with ASD who received a daily dose of 3.7 mg dronabinol experienced more than a 50% decrease in symptoms of irritability, lethargy, hyperactivity, and inappropriate speech as rated by the Aberrant Behavior Checklist (ABC) (12) (*Table 1*).

An observational study that followed 18 ASD patients, aged 7–18, collected information from clinicians and parents assessing a number of symptoms while being treated with a CBD-enriched cannabis oil, using a ratio of 75:1 CBD to THC. Fifteen patients continued treatment for six to nine months and received an average dose of CBD 4.6 mg/kg/day and THC 0.06 mg/kg/day. Results were evaluated by parents as a perceived percentage change for each symptom category as described in the questionnaire. More than 80% of patients reported improvement equal to or above 30% in ADHD, and sleep disorders and seizures; however, 60% of patients also reported a 20% improvement in motor-function disorders, behavioral disorders, communication, and social deficits. In general, adverse effects were mild and transient. They included three cases of sleepiness or irritability, and one case each of diarrhea, increased appetite, conjunctival hyperemia, and increased body temperature. The three patients that stopped treatment early reported insomnia, irritability, increased heart rate, and worsening of neuropsychiatric behavioral symptoms (13) (*Table 1*).

There have also been several large scale open-label studies conducted in Israel of children with ASD receiving oral whole-plant extract at a wide dosing range using a formulation of CBD:THC (20:1). These studies reported improvements in behavioral outbursts, SIB, anxiety, and communication skills (14-16) (*Table 1*). In a recent review of medical cannabis in pediatrics, Aran and Cayam-Rand (37) reported preliminary results from a completed, but still unpublished, double-blind placebo-controlled cross-over study in 150 children and adolescents with ASD (NCT02956226) (38). The investigators compared placebo to two different oral CBD:THC (20:1) formulations; one containing whole-plant extract and the other containing purified CBD and THC. Patients were randomized to receive either placebo or the whole-plant extract formulation for 12 weeks; then, after a four-week washout period, were randomized again to receive either placebo or the purified formulation. The initial dose was 1 mg/kg/day CBD, which was up-titrated until intolerance or to a maximum dose of 10 mg/kg/day, divided into three daily doses. The average dose given was 5.5 mg/kg/day of CBD. They reported a reduction of irritability and core symptoms of autism in both treatment groups when compared to placebo, with no difference between whole-plant extract over purified cannabinoids (37). The most common adverse effects were somnolence and loss of appetite. These results were described in the review by Aran and Cayam-Rand, but have not been published yet and no additional details were provided.

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FASD

Preliminary research implicates the involvement of the ECS in the development of FASD. Basavarajappa *et al.* postulated that alcohol-induced deficits result in disruption of neuronal plasticity, memory processing, and intellectual development (9,39). In one study, the administration of THC, a CB_1 agonist, exacerbated the neurodegenerative properties of alcohol in the neonatal rat brain; the combination of THC and alcohol administration resulted in more significant damage than with alcohol alone. This demonstrates the potential of using a CB_1 antagonist to combat one of the destructive effects of prenatal alcohol exposure on the developing brain: the widespread apoptotic neurodegeneration (40). Although THC in combination with alcohol has demonstrated prenatal destructive behavior in FASD, paradoxically it has been studied as a treatment option for FASD associated behavioral symptoms. A case series investigated cannabis use in two children and three late adolescents with FASD. Doses, formulations, and durations of use between cases varied widely and included CBD oils, smoked THC, and smoked CBD, although none were described in detail. Disruptive symptomatology was ranked by the parent version of the Nisonger Child Behavior Rating Form, a visual analog scale for disruptive symptoms. Each of the subjects exhibited a reduction in disruptive behaviors, such as tantrums, aggressiveness, impulsivity, and anger, as reported by the parent (41) (*Table 1*). More research on the use of cannabis for FASD in children is warranted.

Attention-deficit hyperactivity disorder

Although there are no clinical trials demonstrating the use of cannabis for children with ADHD, the limited results in adults call for additional studies before considering the use in pediatrics. A randomized controlled trial using Sativex®, an oromucosal spray containing a 1:1 ratio of THC and CBD, in adults with ADHD demonstrated efficacy for managing ADHD symptoms including hyperactivity/impulsivity and cognitive inhibition; however, improvement for inattention and emotional lability did not reach statistical significance after multiple testing (41). Although there are not many clinical studies that have investigated the use of cannabis for ADHD, there is anecdotal evidence to suggest that some patients with ADHD may achieve symptom relief through self-medicating with cannabis (42).

Summary statement

Due to the prevalence and severity of behavioral problems associated with ASD, FASD, and ID; and the lack of adequate pharmacological treatment targeting core neuropsychiatric behaviors at this time, alternative therapies are often sought after. Cannabis-derived products, including synthetic and whole plant extracts, have been the subject of several studies to determine efficacy for symptomatic management. Studies have shown promise for the use of high CBD:THC ratios for the treatment of ASD irritability symptoms; however, additional robust controlled trials are needed to establish efficacy in this population. There are very few studies demonstrating benefit for the treatment of specific symptoms of ADHD and FASD symptoms. Therefore, in agreement with others in the field (37), it is recommended that the use of cannabis be limited to severe cases of treatment-resistant irritability in ASD, but further clinical investigation is necessary. To date, there are ongoing double-blind studies in children and young adults with ASD (NCT03202303) (43) and in children and adults with Prader-Willi syndrome (NCT03848481) (44) using cannabidivarin (CBDV), specifically for the management of severe irritability. Notably the high incidence of comorbidities and the overlap in symptoms contribute to the challenges faced when investigators design and conduct studies on ASD, FASD, ADHD, and ID independently. Current published research calls for future clinical studies differentiating these disease states to optimize their treatment.

Movement disorders

Movement disorders encompass an array of diseases associated with the dysfunction of the motor circuit in the basal ganglia. These conditions range from hyperkinetic disorders, such as Tourette syndrome (TS), to neurodegenerative disorders, such as Huntington's disease. These conditions can result in a decreased quality of life (QOL) due to the negative repercussions they have on one's mobility, leading to pain, sleep disturbances, and a decline in mental health (45,46).

Spasticity occurs when the stretch reflex threshold is reduced, resulting in a state of hypertonia (47). Spasticity is often accompanied by limited movement, pain, weakness, changes in posture, and diminished reflexes. Treatment modalities for spasticity include a combination of trigger avoidance, movement and stretching activities, and

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pharmacological agents. Pharmacologic therapies consist of antipsychotics, alpha-adrenergic antagonists, muscle relaxants, and botulinum injections. However, depending on the severity and specific disease state inducing the spasticity, these medications can have limited efficacy (46,48). In this section, the published research will be critically explored to determine the clinical benefit of exogenous cannabinoid products for patients suffering from movement disorders. Theoretically, the THC component in exogenous cannabinoids alleviates movement disorders by acting on the CB_1 receptors in the nervous system, mitigating activity of the excitatory neurotransmitter glutamate (49). This effect leads to the restoration of glutamate and GABA balance, resulting in decreased muscle spasticity.

Complex motor disorders

In a randomized controlled trial by Libzon *et al.* (50), 25 patients, aged 1–16 years, were recruited with a diagnosis of complex motor disorders, including 19 with cerebral palsy, five with neurogenetic syndrome, and one with a traumatic brain injury. The aim was to study the difference in efficacy between varying ratios of CBD and THC on spasticity, dystonia, sleep, mood, constipation, appetite, and QOL. Patients were administered cannabidiol-enriched oils from the Avidekel strain in ratios of 6:1 or 20:1 of CBD:THC for five months. The starting dose was one drop orally three times daily for both formulations, resulting in 6:0.99 mg (6:1) and 6:0.3 mg (20:1) daily. The doses were titrated up on an individual basis until intolerance was observed, a serious adverse effect occurred, a 15 mg/day dose of THC was reached, or the study ended. All prior concurrent medications were continued. Patients were assessed using standardized questionnaires and parental evaluation, initially to establish a baseline and then every month thereafter. Results demonstrated statistically significant improvement for both formulations in spasticity (6:1 P=0.011; 20:1 P=0.048) and QOL (6:1 P=0.011; 20:1 P=0.023) with a median THC dosing range of 0.44 mg/kg/d for reduction of spasticity. The 6:1 formulation also showed statistically significant improvement in motor function (P=0.047) and sleep (P=0.011), while the 20:1 was significant in the numeric rating scale for dystonia (P=0.036), the Barry Albright Dystonia Scale (P=0.021) and stool function (P=0.011). Mean dosages for improvement of QOL in the 6:1 formulation were 3.73:0.61 mg/kg/d (CBD:THC), while the 20:1 group showed improvement in dystonia and QOL with mean dosages of 5.53:0.28 mg/kg/d (CBD:THC).

Adverse effects included behavioral changes, including excitation and mood fluctuations (one patient in each group), somnolence (6:1 group at a dose of 1.8:0.3 mg/kg/d CBD:THC), and worsening seizures (group unspecified). There was no worsening of hepatic aminotransferase levels during the study period. Of the 20 patients that completed this study, 15 participants continued with treatment.

Refractory spasticity

An open-label, uncontrolled, retrospective study investigated the use of oral dronabinol 2.5% drops as adjunct therapy for palliative care in 16 children, adolescents, or late adolescents with refractory spasticity. Doses ranged from 0.08 to 1 mg/kg/day and started at one drop (0.83 mg) twice daily for all patients. Titration of an added 0.83-mg/day occurred every three days. Although there was no use of standardized tools to evaluate symptomatic benefit, improvement was indicated when the parents, nurses, or physiotherapists determined that caring for the patient was easier. Duration of treatment ranged from 23 days to four years. Of the 16 patients, 12 showed symptomatic improvement in symptoms with dronabinol use. Adverse effects were rare, but two patients withdrew from the study due to vomiting and restlessness (one patient each). It is important to acknowledge that none of the patients included were verbally communicative, and as a result, psychological changes were not evaluated. Of the remaining 14 patients, 10 continued with treatment and four died from complications related to their illness (51).

Tourette syndrome (TS)

TS is a neuropsychiatric disorder that usually develops around 5–8 years of age and is characterized by motor and vocal tics, which can be simple or complex (52). Tics can disrupt cognitive behaviors and ASD or ADHD are common comorbidities. ADHD concurrently exists in as many as 60% of patients with TS, significantly affecting QOL (53). The specific etiology and pathology of TS remains unexplained; however, neurological pathophysiologic studies suggest that disturbances in various neurotransmitter systems may play a role in the pathophysiology of TS disorder. Abnormal functioning of dopaminergic, glutamatergic, serotonergic, and GABAergic signaling pathways may contribute to the manifestation of symptoms, which are commonly vocal and muscular tics (54,55). Due to the primary hypothesis of abnormal

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dopamine transmission in the nigrostriatal pathway, dopamine antagonists have been used for symptom management. Haloperidol, pimozide, and aripiprazole are the only FDA approved drugs for use in TS. Tiapride and sulpiride, which typically cause less adverse effects, are used in Europe and Asia (56). Although atypical antipsychotics have data supporting their efficacy in TS, they are often not given as first line agents to the pediatric population due to their adverse effect profile, which includes weight gain, metabolic syndrome, and extrapyramidal symptoms (56). Consequently, therapeutic intervention usually begins conservatively with psycho-education and behavioral therapies. Other pharmacologic therapy includes the off-label use of alpha$_2$-agonists (e.g., clonidine) due to the inhibition of sympathetic outflow and their relatively benign side effect profile (56).

Research on the use of cannabinoids began after reports of tic improvement in patients who used inhaled cannabis (57). Due to the extensive involvement of the ECS and neurotransmitter regulation, it is thought that CB_1 receptor dysfunction in the central nervous system may be responsible for TS symptoms; therefore, endocannabinoids and exogenous cannabinoids may regulate signaling activity of neurotransmitters that are implicated in TS, such as glutamate, GABA, serotonin, and noradrenaline (48). In addition, the ECS may have an inhibitory effect on dopaminergic pathways, mitigating the effects of overactive dopamine transmission, which may be implicated in the pathology of TS (54).

Three pediatric case reports have been published pertaining to the use of exogenous cannabinoids for treating TS. In one case, a 15-year-old with refractory TS and comorbid ADHD was initiated on an oral THC dose of 5 mg/day and titrated up to a dose of 15 mg/day within three weeks. After seven weeks, the patient exhibited a decrease in Yale Global Tic Severity Scale scores, improved QOL, as measured by the Guilles de la Tourette Syndrome-Quality of Life scale, and providers were able to successfully initiate stimulant treatment for ADHD symptoms. There were no adverse effects reported, except for a mild episode of euphoria that occurred after the first dose (57).

A second case report described a highly impaired 7-year-old with TS and ADHD who received oral THC, starting at 0.7-mg/day to augment his conventional therapy. THC was increased over the next two months to 5.4-mg/day, resulting in a tic reduction of 50%. Dosing was then slowly titrated to 18.2-mg twice daily after four weeks. Assessment showed an improvement in mood, stress, general impairment, and QOL, corresponding with a gradual withdrawal of risperidone. Somnolence was noted as an adverse effect, however, this improved over time (58). A third case report showed improvements in a 12-year-old with severe TS after parent-initiated THC treatment. They began with vaporized cannabis with an equivalent THC dose of 4.4 mg, transitioning to oral THC drops at a maximum of THC 34.5-mg/day. Both parents and clinicians reported reduction of tics and overall impairment and no adverse events were observed (59).

Summary statement

The available published data suggest that exogenous cannabinoids may provide benefits for the alleviation of spasticity symptoms, with the greatest effect seen when used as adjunct therapy for TS and refractory spasticity. Although sufficient data are lacking, some studies have demonstrated benefits of cannabis-derived products in the management of spasticity as add-on therapy in pediatric patients not adequately responding to other medications. Treatment was generally well-tolerated with the most common adverse reaction being somnolence. The products used ranged widely and included dronabinol, CBD:THC combinations, oral THC, and inhaled cannabinoids.

Pain associated with movement disorder

Patients with motor and tic disorders often experience physical pain due to excessive contraction or spasticity from repeated movements. However, pain may also be a result from striking the moving body part against nearby objects or from voluntary efforts to suppress the tic. Although the pain is usually musculoskeletal in nature, neuropathic pain may also occur with spinal cord or peripheral nerve compression (60). Pain relief, in addition to improving the QOL by decreasing abnormal movement, is an important therapeutic goal for motor disorders and spasticity (61).

The fundamental approach to the management of pain due to spasticity or excessive contractions is to resolve the underlying spasticity. This can be accomplished with the use of both non-pharmacological and pharmacological agents. Non-pharmacologic pain regimens include heat and cold compresses, transcutaneous electrical nerve stimulation, electrotherapy, and hydrotherapy. Drug therapy with analgesics, anti-inflammatory agents, and tricyclic antidepressants may be useful; and anticonvulsants, such as carbamazepine and gabapentin, have also been used,

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but with limited success (61). However, if treatment of the underlying condition is insufficient to control the associated pain, physicians may recommend additional therapy specific for pain relief. The limited availability of pharmacologic agents available to effectively manage pain caused by spasticity prompt the need for alternative therapy, such as cannabis.

CB_1 receptors are located in nociceptive regions of the peripheral and central nervous system and are associated with the processing and modulation of pain (62). In addition, immune cells, including macrophages and mast cells, and epidermal keratinocytes express CB_1 receptors. CB_2 receptors are found mostly in peripheral immune cells and tissues, but also in brain microglia; as a result, CB_2 receptors modulate chronic pain and inflammation by inhibiting the release of cytokines and the migration of neutrophils and macrophages. Cannabinoids have the potential to mitigate neuropathic pain as both CB_1 and CB_2 receptors have been found to be upregulated in response to peripheral nerve damage (63). Through the activation of CB_1 and CB_2 receptors, cannabinoids have demonstrated analgesic and anti-inflammatory effects as well as the alleviation of neuropathic pain (62).

In the study by Libzon of 25 children, CBD-enriched oil significantly improved spasticity as well as pain for the total study cohort, the latter assessed by the visual analog score (50). Another survey-based study of families with children experiencing pantothenate kinase-associated neurodegeneration demonstrated that topical and oral cannabis products were commonly used in children with more severe dystonia and pain associated with the disorder. Pain improvement was reported with the use of cannabis and many of the families perceived cannabis to be helpful for dystonia, pain, anxiety, and sleep (64). In one case report, oral cannabis at an unknown dose was started in a 6-year-old female with a severe hypoxemic brain injury to treat her intractable seizures and neuropathic pain secondary to spasticity and contractures. Her family noted that the patient experienced pain relief with the initiation of cannabis (65).

Summary statement

Notably all patients in studies of pain associated with movement disorder demonstrated some improvement in pain with the use of cannabis. Although the American Academy of Pediatrics does not formally recommend the use of medical marijuana in children and adolescents, cannabinoid medications are commonly self-initiated and used to treat pain secondary to spasticity or motor disorders in children. With positive results of pain relief, cannabis seems promising for use in children with pain secondary to severe or complex motor disorders and requires further research. It should be noted that the children in these case reports and studies had severe and complex motor disorders, greatly impacting their daily lives. For these families, the goal of treatment is pain relief and improvement in their QOL. Therefore, the benefits of cannabis sometimes outweigh the potential neurological risks and may be considered in the management of pain associated with spasticity in patients refractory to conventional therapies. However, the use of cannabis for this indication requires further research.

Pain in epidermolysis bullosa (EB)

EB is a group of congenital conditions that predispose patients to blistering of the skin and mucosa upon mechanical trauma or friction. EB consists of four subtypes and each may vary in severity, ranging from a minor inconvenience that requires modification of daily activities to debilitating pain that can prevent ambulation (66). Patients with EB tend to have poor QOL due to acute and chronic pain from the formation of blisters on any surface of the skin. In addition, patients are burdened with intense pain and itching on a daily basis (67). With the absence of a cure for EB, supportive care is recommended and includes wound care and the management of pain and pruritus.

The current guidelines for the treatment of EB focus both on non-pharmacologic and pharmacologic interventions. Non-pharmacologic methods include cognitive behavioral therapy such as distraction, hypnosis, visualization, or relaxation for acute and chronic pain and habit reversal training for pruritus. Pharmacologic therapies include opioids, tramadol, non-steroidal anti-inflammatory drugs, and acetaminophen for pain. Antihistamines, gabapentin, pregabalin, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors are recommended to relieve itching (67,68). However, these pharmacologic agents may fail to provide adequate analgesia and antipruritic response for some patients; thus, these patients may require an alternative therapy to improve their QOL.

The human skin has the ability to synthesize and respond to cannabinoids via cannabinoid receptors (CB_1 and CB_2) that are expressed in the epidermal layer of the skin and

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its appendages. Both of these receptors are located in keratinocytes, melanocytes, sebaceous glands, hair follicles, sensory nerve cells, and immune cells (68,69). The functions of cannabinoid receptors include regulation of proliferation and differentiation of keratinocytes, modulating the sensation of pain and itch, and decreasing Th2 response and the production of pro-inflammatory cytokines to reduce inflammatory responses (70).

With its ability to modulate the debilitating symptoms of pain and pruritus in EB, cannabinoid medication is an alternative that is commonly self-initiated by parents for their children. CBD oil was self-initiated in three children with diagnosed EB. In all three cases, parents initiated topical CBD without recommendations from a physician. A tincture of CBD oil was sprayed onto affected areas two to three times daily for one patient and a CBD oil blend was applied to the blisters of the second patient at least twice daily. The frequency of application of a CBD oil and cream to the third patient was unclear. Although the specific formulations, dosages and duration of cannabis use was not described, family members in all three patients reported a noticeable reduction in blistering, faster healing time, and relief of pain, resulting in improvement of ambulation and overall QOL. With the initiation of topical CBD, two patients were able to stop the use of oral analgesic medications; diphenhydramine and morphine in one case and naproxen and gabapentin in the other (71).

Summary statement

Anecdotal data from case studies have shown that topical CBD can help alleviate pain caused by EB. As the risk of using topical CBD is low, cannabidiol oil may be considered as an alternative in patients with EB who failed to achieve adequate pain control with standard therapies.

Conclusions

Published research suggests potential benefits for the use of cannabis in the treatment of neuropsychiatric conditions, movement disorders, and pain. The inconsistency and wide range of cannabis products administered in current studies underscores the need for standardization of formulations and doses appropriate for children. Based on current studies, cannabis may be considered as adjunct therapy for movement disorders and its associated pain when patients have failed recommended therapies; however, more studies are needed to establish optimal dosing and duration of therapy, with ascertainment of the use of cannabis as monotherapy. Topical CBD may be considered as an alternative in patients with EB when recommended therapies do not provide adequate pain control. Currently, there are insufficient data in the pediatric population to recommend the use of cannabis for neuropsychiatric conditions.

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Footnote

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