

Medical Cannabinoids in Children and Adolescents: A Systematic Review

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abstract

CONTEXT: Legalization of medical marijuana in many states has led to a widening gap between the accessibility and the evidence for cannabinoids as a medical treatment.

OBJECTIVE: To systematically review published reports to identify the evidence base of cannabinoids as a medical treatment in children and adolescents.

DATA SOURCES: Based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a search of PubMed, Medline, and the Cumulative Index to Nursing and Allied Health Literature databases was conducted in May 2017.

STUDY SELECTION: Searching identified 2743 citations, and 103 full texts were reviewed.

DATA EXTRACTION: Searching identified 21 articles that met inclusion criteria, including 22 studies with a total sample of 795 participants. Five randomized controlled trials, 5 retrospective chart reviews, 5 case reports, 4 open-label trials, 2 parent surveys, and 1 case series were identified.

RESULTS: Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting, with increasing evidence of benefit for epilepsy. At this time, there is insufficient evidence to support use for spasticity, neuropathic pain, posttraumatic stress disorder, and Tourette syndrome.

LIMITATIONS: The methodological quality of studies varied, with the majority of studies lacking control groups, limited by small sample size, and not designed to test for the statistical significance of outcome measures. Studies were heterogeneous in the cannabinoid composition and dosage and lacked long-term follow-up to identify potential adverse effects.

CONCLUSIONS: Additional research is needed to evaluate the potential role of medical cannabinoids in children and adolescents, especially given increasing accessibility from state legalization and potential psychiatric and neurocognitive adverse effects identified from studies of recreational cannabis use.

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Dr Wong conceptualized and designed the study, collected the data, conducted the initial analyses, and drafted the initial manuscript; Dr Wilens conceptualized and designed the study and supervised data collection; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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TABLE 1 Cannabis Products

Products Generic (Brand)	Cannabinoid Content	Administration Formulation and Dosage	FDA Approval	Indications	Approved Countries
Dronabinol (Marinol and Syndros)	Synthetic δ -9-THC	Oral capsule or solution 5–15 mg/m ² per dose, up to 6 doses daily	Approved in 1985, Schedule III controlled substance	CINV (pediatric and adult), anorexia associated with weight loss in AIDS (adult)	United States, Australia, Germany, New Zealand, and South Africa
Nabilone (Cesamet)	Synthetic δ -9-THC	Oral capsule 1 or 2 mg twice a day, up to 6 mg daily (adult)	Approved in 1985, Schedule II controlled substance	CINV	United States, Canada, Ireland, Mexico, and United Kingdom
Nabiximols (Sativex)	Ratio of 2.7 δ -9-THC to 2.5 CBD, plant derived	Oromucosal spray 1 spray daily, up to 12 sprays daily with at least 15 min between sprays (adult)	Phase III trials	Neuropathic pain, cancer pain, multiple sclerosis spasticity	Canada, Czech Republic, United Kingdom, Denmark, Germany, Poland, Spain, and Sweden
CBD (Epidiolex)	CBD, plant derived	Oral solution 2 up to 50 mg/kg per d (research trials)	Phase III trials, fast-track designation	Epilepsy	None
Cannabis plant products (eg, marijuana and oral cannabis extracts)	Varying concentration of plant-derived THC to CBD	Includes smoking (marijuana) and oral (cannabis extracts)	None, Schedule I controlled substance	None approved	Medically and recreationally legal in certain states via physician certification

Cannabis is a plant that produces pharmacologically active cannabinoids, of which the constituents cannabidiol (CBD) and tetrahydrocannabinol (THC) are the most studied.¹ CBD may function via a variety of mechanisms, including indirect antagonism and potentiation of cannabinoid receptors, whereas THC acts primarily as a partial agonist to cannabinoid receptors.

Within the THC class of cannabinoids, δ -9-THC is the primary form found in cannabis, whereas δ -8-THC is prepared by cyclization and has less psychotropic potency.

Currently, there are 2 synthesized cannabinoids that the Food and Drug Administration (FDA) has approved as medications in the United States, dronabinol and nabilone, both of which mimic δ -9-THC. These 2 medications are the only current cannabinoids available by physician prescription. For pediatric populations, dronabinol dosage for chemotherapy-induced nausea and vomiting (CINV) is the same as for adults. However, dronabinol use for AIDS-related anorexia as approved in adults is not recommended

in children because of a lack of pediatric studies, with further caution recommended because of psychoactive effects.² Similarly, the use of nabilone is cautioned in pediatric patients because of psychoactive effects and a lack of established safety and effectiveness.³

On the other hand, naturally derived products from cannabis include marijuana (dried leaves and flowers that are most commonly smoked) and oral cannabinoid extracts, and such products have varying concentrations of cannabinoids (eg, CBD and THC) depending on the strain of the plant. There are also 2 plant-derived cannabinoid medications with standardized THC and CBD content currently undergoing FDA-regulated clinical trials, nabiximols and a CBD oral solution (See Table 1 for a summary of cannabis products).

Because of state legalization of medical marijuana, the medical use of naturally derived products from cannabis, including marijuana and oral cannabinoid extracts, is now legal in more than half of US states via physician certification.

All states with operational medical marijuana programs allow use by minors but require consent from a legal guardian and certification from a physician.⁴ Certain states require the consenting guardian to control the acquisition, dosage, and frequency of use (ie, AK, AZ, HI, ME, MI, NH, NM, NY, OR, RI, and Washington, DC). Additionally, some states require a second physician for the certification of a minor's use (ie, CT, CO, DE, FL, IL, MA, ME, MI, MT, NH, and NJ), including 4 states that require specific certification from a pediatrician (ie, MA and NH), pediatric subspecialist (ie, DE), or pediatrician and psychiatrist (ie, NJ).

The legalization of medical marijuana has led to a widening gap between its accessibility and the limited evidence base for medical cannabinoids as a treatment of pediatric populations. Currently, the American Academy of Pediatrics opposes dispensing medical cannabis to children and adolescents outside the regulatory process of the US FDA, although the Academy does recognize that cannabis may currently be an option for cannabinoid administration for

Cannabinoids: cannabinoids[MeSH Terms] OR cannabis[MeSH Terms] OR cannabidiol OR delta-8-tetrahydrocannabinol OR dronabinol OR marijuana[MeSH Terms] OR "marijuana smoking/therapy"[MeSH Terms] OR "marijuana smoking/therapeutic use"[MeSH Terms] OR "medical marijuana" OR nabilone OR tetrahydrocannabinol-cannabidiol combination.

Youth: pediatric OR child[MeSH Terms] OR adolescent[MeSH Terms].

Key domains are listed above in italics. Domains were joined using the Boolean operator

“AND”.

FIGURE 1

Sample search strategy (PubMed).

children with life-limiting or severely debilitating conditions and for whom current therapies are inadequate.⁵ The purpose of this review is to systematically examine the current evidence for using cannabinoids as a medical treatment in children and adolescents.

METHODS

A systematic review of the literature on medical cannabinoids in children and adolescents was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁶ Medline, PubMed, and the Cumulative Index to Nursing and Allied Health Literature were searched for studies published from 1948 to 2017 and indexed by May 2017 by using the following medical subject heading terms and keywords (listed alphabetically): “cannabinoids,” “cannabis,” “CBD,” “ δ -8-THC,” “dronabinol,” “marijuana,” “marijuana smoking/therapy,” “marijuana smoking/therapeutic use,” “medical marijuana,” “nabilone,” and “THC-CBD combination.” Each was cross-referenced with child, adolescent, or pediatric keywords (see Fig 1 for a sample search strategy with Boolean search parameters).

Given the preliminary stage of research in this area, only minimal exclusion criteria were used. Studies were included if they were primary research that reported original data, examined the benefits of cannabis for a clinical indication (ie, all medical disorders), in English, and comprised of a child and adolescent patient sample. Studies were excluded if the majority of the sample was older than 18 years or if age and/or data for children and adolescents were not reported separately.

One independent reviewer (S.S.W.) assessed study eligibility by screening the titles, abstracts, and full-text articles in a standardized manner. Both investigators for final inclusion then reviewed the resulting full-text articles, with summarized information focusing on details such as clinical indication, cannabinoid type, sample characteristics, methodological design, and outcome. For cases in which primary outcomes were not specified, only the most frequently reported outcome was reported.

RESULTS

Medline, PubMed, and the Cumulative Index to Nursing and Allied Health Literature searches yielded 2743

citations. After adjusting for duplicates ($n = 132$), 2611 citations remained. Of these, 2508 were excluded, with the most common reasons for exclusion being an article without information about clinical use ($n = 1832$), an article without original data ($n = 574$), an article not relating to cannabis ($n = 78$), and an article not available in English ($n = 24$). The remaining 103 citations were assessed for eligibility by reviewing the full-text articles, and 82 were excluded because of the majority of the sample being older than 18 years or the data for children and adolescents were not reported separately. A total of 21 articles describing 22 studies were identified for final inclusion. A flow diagram is provided in Fig 2.

Study Characteristics

The 21 articles identified dated from 1979 to 2017, with 14 of the studies published within the last 5 years. Five randomized controlled trials (RCTs), 5 retrospective chart reviews, 5 case reports, 4 open-label trials, 2 parent surveys, and 1 case series were identified. The total number of participants across all studies was 795. Of the 5 medical conditions studied, the most common indication was for seizures ($n = 11$) and CINV

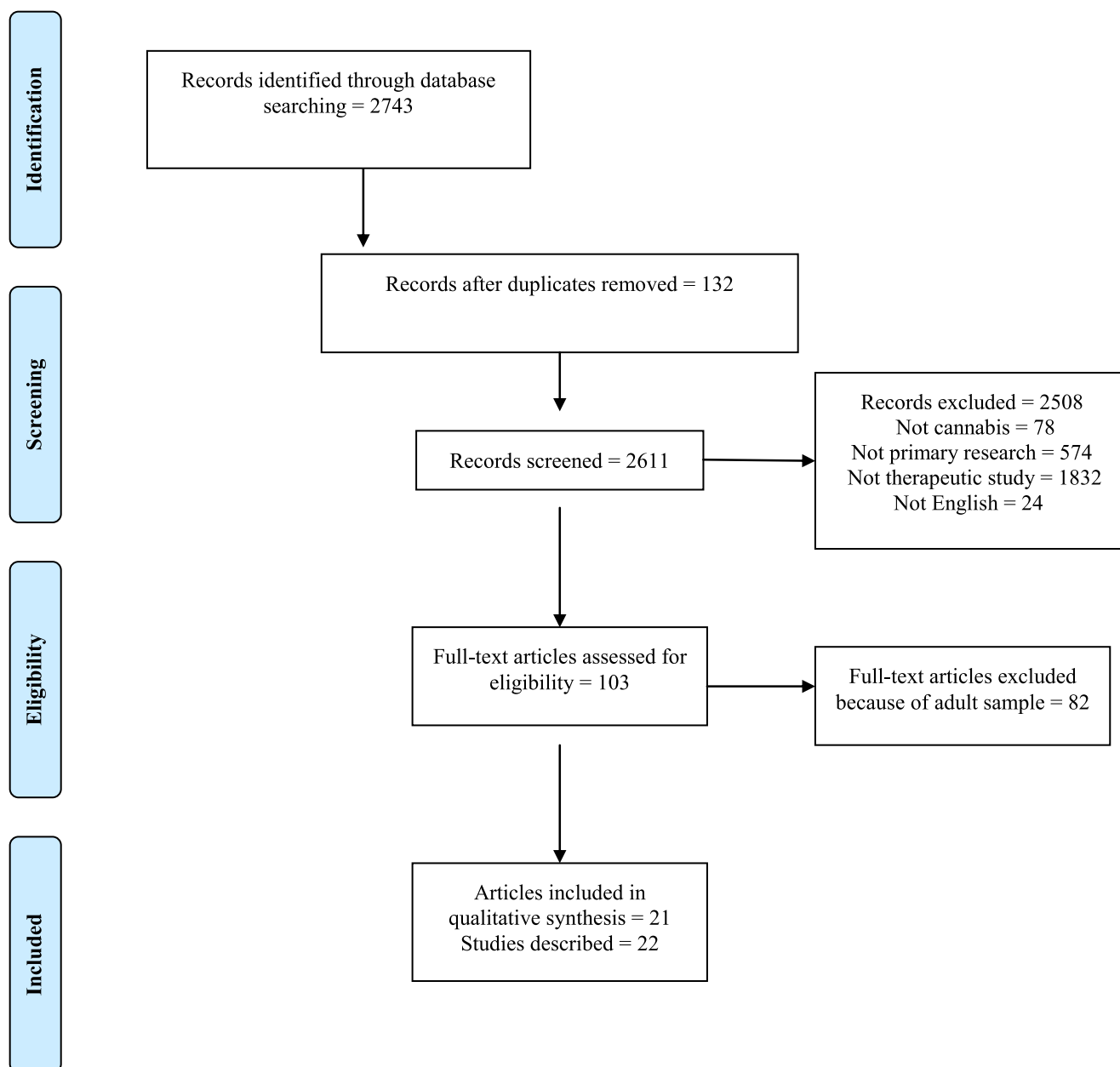


FIGURE 2
Flow diagram of search history.

($n = 6$), followed by spasticity ($n = 2$), tics ($n = 1$), posttraumatic stress disorder (PTSD) ($n = 1$), and neuropathic pain ($n = 1$). Data abstraction followed the PRISMA guidelines. Table 2 summarizes the studies by clinical indication, sample characteristics, cannabinoid type, measures, and outcomes. Table 3 presents additional clinical descriptions of findings from each study, including cannabinoid dosage,

frequency, formulation, secondary outcomes, and side effects.

Medical Cannabinoids for CINV

There have been 6 studies of cannabinoids for the treatment of CINV in children and adolescents. Dalzell et al¹⁰ showed that nabilone decreased nausea severity and frequency of vomiting in comparison with domperidone in a double-blind, crossover RCT of 23 children. Over

a 5-day cycle of chemotherapy, patients treated with nabilone had an average of 6 episodes of emesis in comparison with 17 episodes of emesis among patients given domperidone. Nabilone also reduced nausea severity rated as 1.5 on a 5-point scale in comparison with a 2.5 severity rating in the domperidone treatment group. In a subsequent double-blind, cross-RCT of 30 children, Chan et al⁹ reported

TABLE 2 Pediatric Studies of Medical Cannabinoids

Study by Indication Authors, y	Sample Size	Diagnoses (Inclusion Criteria)	Mean Age (Range)	Design	Medication	Measures	Findings
CINV							
Elder and Knoderer, ⁷ 2015	58	Childhood cancer	13.9 (6–18)	Retrospective chart review	Dronabinol	Episodes of vomiting	Positive response (0–1 bouts of vomiting) in 60% of children
Abrahamov et al, ⁸ 1995	8	Hematologic cancers	6.6 (3–13)	Open-label trial	Δ-8-THC	Episodes of vomiting	Prevented vomiting in all 480 total treatment cycles
Chan et al, ⁹ 1987	30	Childhood cancer	11.8 (3.5–17.8)	Double-blind, crossover RCT	Nabilone	Episodes for retching and vomiting	Reduced retching and vomiting compared with prochlorperazine
Dalzell et al, ¹⁰ 1986	23	Childhood cancer	7.9 (0.8–17)	Double-blind, crossover RCT	Nabilone	Episodes of vomiting, nausea scale (0–3)	Reduced nausea severity and vomiting compared with domperidone
Ekert et al, ¹¹ 1979	19 and 14	Childhood cancer	12.5 (5–19)	Two double-blind RCTs	Δ-9-THC	Episodes of nausea and vomiting	Reduced nausea and vomiting compared with metoclopramide or prochlorperazine
Epilepsy							
Devinsky et al, ¹² 2017	61	Treatment-refractory epilepsy in Dravet syndrome	9.8 y (2.3–18.4)	RCT	CBD	Convulsive-seizure frequency	Reduced convulsive seizures compared with a placebo
Gofshiteyn et al, ¹³ 2017	7	FIRES ^a	7.1 (3.9–8.5)	Open-label trial	CBD	Seizure frequency and duration, EEG	Reduced seizures in 86% of patients
Kaplan et al, ¹⁴ 2017	5	Treatment-refractory epilepsy in SWS	8.8 (2–19)	Open-label trial	CBD	Seizure frequency	Seizures improved in 60% of patients
Treat et al, ¹⁵ 2017	119	Epilepsy	7.5 (0.1–18)	Retrospective chart review	OCE	Seizure frequency	Seizures improved in 49% of patients, with 24% responders (>50% reduction)
Devinsky et al, ¹⁶ 2016	137	Treatment-refractory epilepsy	10.5 (1–22.2)	Open-label trial	CBD	No. of seizures, LAEP, PESQ	37% decrease in monthly motor seizures
Tzadok et al, ¹⁷ 2016	74	Treatment-refractory epilepsy	1–18	Retrospective chart review	CBD-enriched OCE	Seizure frequency	Reduced seizures in 89% of patients
Hussain et al, ¹⁸ 2015	117	Treatment-refractory epilepsy	6 (3–10)	Parent survey	CBD-enriched OCE	Seizure frequency	Reduced seizures in 85% of patients
Press et al, ¹⁹ 2015	75	Treatment-refractory epilepsy	7.3 (0.5–18.3)	Retrospective chart review	OCE	Seizure frequency	Reduced seizures in 57% of patients
Saade and Joshi, ²⁰ 2015	1	MMPSI ^a	10 mo	Case report	CBD	Seizure frequency, EEG	Reduced seizure frequency
Porter and Jacobson, ²¹ 2013	19	Treatment-refractory epilepsy	9.1 (2–16)	Parent survey	CBD-enriched OCE	Seizure frequency	Reduced seizures in 84% of patients
Lorenz, ²² 2004	6	Neurodegenerative disease, mitochondriopathy, posthypoxic state, epilepsy	12.3 (8.8–14)	Case series	Dronabinol	Seizures	Reduced seizures in 2 of the patients
Neuropathic pain^a							
Rudich et al, ²³ 2003	2	Comorbid MDD	14.5 (14–15)	Case report	Dronabinol	0–100 numerical rating scale	Forty percent to 60% reduction in the affective component of pain
PTSD							
Shannon and Opila- Lehman, ²⁴ 2016	1	Comorbid anxiety, insomnia, prenatal cannabis exposure	10	Case report	CBD	SCARED, SDSC	Decreased anxiety and improved sleep
Spasticity^a							
Kuhlen et al, ²⁵ 2016	16	Neurodegenerative disease, CNS syndromes, asphyxia	11.4 (1.3–26.6)	Retrospective chart review	Dronabinol	Spasticity	Reduced spasticity in 75% of patients
Lorenz, ²⁶ 2002	1	NCL	3.3	Case report	Dronabinol	Spasticity, myoclonus	Reduced spasticity and myoclonus

TABLE 2 Continued

Study by Indication Authors, y	Sample Size	Diagnoses (Inclusion Criteria)	Mean Age (Range)	Design	Medication	Measures	Findings
Hasan et al ²⁷ , 2010	1	Comorbid ADHD	15	Case report	Δ-9-THC	YGTSS, GTS-QoL, CTRS-R-L	Decreased tic severity, improved quality of life

ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; CTRS-R-L, Conners' Teacher Rating Scale—Revised; Long. FIRES, febrile infection-related epilepsy syndrome; GTS-QoL, Gilles de la Tourette Syndrome—Quality of Life Scale; LAEP, Liverpool Adverse Events Profile; MDD, major depressive disorder; MMPSI, malignant migrating partial seizures of infancy; NCL, neuronal ceroid lipofuscinosis; OCE, oral cannabis extract; PESQ, Pediatric Epilepsy Side Effects Questionnaire; SCARED, Screen for Child Anxiety Related Disorders; SDSC, Sleep Disturbance Scale for Children; SWS, Sturge-Weber syndrome; YGTSS, Yale Global Tic Severity Scale.

^a Treatment-refractory condition.

nabilone improved retching and emesis by 70% compared with 30% with prochlorperazine. Over a cycle of chemotherapy, patients experienced 13 episodes of retching or emesis in comparison with 27 episodes when given prochlorperazine. In an article reporting on 2 double-blind RCTs, Ekert et al¹¹ showed that δ-9-THC reduced nausea and vomiting in comparison with metoclopramide as well as prochlorperazine.

In an open-label trial, Abrahamov et al⁸ reported that δ-8-THC prevented vomiting during 480 cycles of chemotherapy among 8 children when given 2 hours before chemotherapy and repeated every 6 hours. In a more recent retrospective chart review of 95 children, Elder and Knoderer⁷ reported that dronabinol treatment given a median of 3 times over the course of chemotherapy led to a positive response in 60% of children (0–1 bouts of emesis). Notably, 95% of patients received lower dosing than was guideline referred (5 mg/m²), with the most common dose given being 2.5 mg/m² every 6 hours as needed. Two-thirds of patients received repeated courses, and 62% received outpatient prescriptions, suggesting good tolerability of the medication.

Medical Cannabinoids for Epilepsy

There have been 11 studies of medical cannabinoids for the treatment of seizures in children and adolescents. In a recent RCT, Devinsky et al¹² found that CBD significantly reduced convulsive seizure frequency in children with treatment-resistant epilepsy in Dravet syndrome as compared with a placebo. Among 61 participants who received CBD, the median frequency of monthly convulsive seizures decreased from 12.4 seizures per month to 5.9 seizures per month, as compared with a decrease of 14.9 to 14.1 in the placebo group. This represented an adjusted reduction in median seizure frequency by

22.9% with CBD in comparison with a placebo. Fifteen percent of those in the CBD group discontinued treatment before the 14 weeks as compared with 5% of those in the placebo group.

In a previous open-label trial, Devinsky et al¹⁶ reported that CBD reduced seizure frequency in a pediatric population with childhood-onset treatment-resistant epilepsies from a range of different causes. In the efficacy analysis of 137 completers over the 12-week treatment period, CBD led to a clinically relevant reduction in seizures with a median decrease in monthly motor seizures of 37%, from a baseline median of 30 motor seizures monthly to 16 motor seizures monthly. There was a low rate of patient discontinuation of CBD because of poor efficacy (3%). CBD also had acceptable tolerability, with only 3% of patients discontinuing treatment because of an adverse event. Notably, 24% of enrolled patients were not included in the safety analysis because of <12 weeks of treatment or follow-up.

In a small open-label case series of CBD for patients with treatment-refractory epilepsy in Sturge-Weber syndrome, Kaplan et al¹⁴ reported that seizures were reduced in 3 of the 5 patients. In a similar open-label case series of CBD for patients diagnosed with febrile infection-related epilepsy syndrome, Gofshteyn et al¹³ reported that seizures were reduced in 6 of the 7 patients.

In a retrospective chart review of 119 pediatric patients with epilepsy, Treat et al¹⁵ reported oral cannabis extracts improved seizures in 49% of the cohort, with 24% of the patients considered responders as defined by a >50% reduction in seizure burden. In a second retrospective chart review from the same institution, Press et al¹⁹ found that oral cannabis extracts reduced seizures in 57% of the 75 patients with treatment-refractory seizures. Tzadok et al¹⁷

TABLE 3 Clinical Description of Findings From Pediatric Studies of Medical Cannabinoids

Study by Indication Authors, y	Duration of Treatment and Follow-up	Medication Dosing, Frequency, and Formulation	Primary and Secondary Outcomes	Side Effects	Additional Clinical Findings
CINV Elder and Knoderer, ⁷ 2015	Duration of inpatient hospitalization for chemotherapy	Most common dronabinol dose was 2.5 mg/m ² Q6H, scheduled in 55% and PRN in 45% of patients Ninety-five percent received lower doses than guideline referred (5 mg/m ²) Median 3.5 doses received during hospitalization (range 1–129) Δ-8-THC dose of 18 mg/m ² 2 h before chemotherapy, repeated Q6H hours for 4 total doses Δ-8-THC prepared from CBD by cyclization, has 25%–50% less psychotropic potency than δ-9-THC Oil drops-based solution Nabilone oral capsule 0.5–2 mg BID (by weight)	Sixty percent of children had a positive response (0–1 bouts of emesis), 13% had a fair response (2–3 bouts), and 27% had a poor response (>4 bouts)	Not available	Sixty-five percent received repeated courses, and 62% received outpatient prescriptions, suggesting good tolerability
Abrahamov et al, ⁸ 1995	Four hundred eighty 24-h chemotherapy cycles	Oil drops-based solution Nabilone oral capsule 0.5–2 mg BID (by weight)	Prevented vomiting in all treatment cycles In 2 treatment cycles in which δ-8-THC was declined, repeated vomiting occurred. Subsequent cycles with δ-8-THC prevented vomiting	Irritability (n = 2) and euphoria (n = 1)	Preliminary trials with only the first 1–2 doses of δ-8-THC led to vomiting in most cases
Chan et al, ⁹ 1987	Two consecutive, identical cycles of chemotherapy in a crossover design	Prochlorperazine 2.5–5 mg BID Nabilone oral capsule 0.5 mg BID (by weight)	Nabilone decreased retching and emesis in 70% of patients compared with prochlorperazine (30%, P = .003) Nabilone decreased total episodes of retching or emesis compared with prochlorperazine (13 vs 27 episodes; P < .05)	Drowsiness (67%), dizziness (50%), euphoria (11%), ocular swelling and/or irritation (11%), and orthostatic hypotension (8%)	Sixty-six percent preferred nabilone compared with 17% who preferred prochlorperazine (P = .015) Sixty-six percent continued nabilone in the open-label study, with no evidence of tolerance
Dalzell et al, ¹⁰ 1986	Five-d course of chemotherapy in each arm of the crossover design	Nabilone oral capsule 0.5 mg BID to 1 mg TID (by weight) Domperidone 5–15 mg TID (by weight)	Nabilone reduced vomiting episodes per chemotherapy cycle (5.9 vs 16.7, P < .01), and nausea severity rating (1.5 vs 2.5, scaled 0–3; P = .01) in comparison with domperidone	Drowsiness (55%), dizziness (35%), elevated mood (14%), and hallucinations (n = 1)	Sixty-six percent preferred nabilone and 6% preferred domperidone (P < .01)

TABLE 3 Continued

Study by Indication Authors, y	Duration of Treatment and Follow-up	Medication Dosing, Frequency, and Formulation	Primary and Secondary Outcomes	Side Effects	Additional Clinical Findings
Ekert et al, ¹¹ 1979	Consecutive chemotherapy courses randomly assigned to THC or control antiemetic	<p>Δ-9-THC 10 mg/m², up to maximum dose of 15 mg</p> <p>Metoclopramide 5 or 10 mg (BSA >0.7 m²)</p> <p>Prochlorperazine 5 or 10 mg (BSA dependent)</p> <p>Schedule for antiemetic dosing 2 h before and 4, 8, 16, and 24 h after chemotherapy except placebo is given instead of control antiemetic at 4 h to prevent neurologic toxicity</p>	<p>Δ-9-THC reduced nausea (6 vs 21 episodes) and completely prevented vomiting (12 vs 5 cycles) compared with metoclopramide ($P < .01$).</p> <p>Δ-9-THC reduced nausea (6 vs 18 episodes) and completely prevented vomiting (9 vs 0 cycles) compared with prochlorperazine ($P < .001$)</p>	<p>Increased drowsiness ($P > .02$) and less anorexia ($P > .05$) compared with metoclopramide</p> <p>Increased appetite ($n = 7$)</p> <p>One patient had agitation, anxiety, and bad dreams and refused further THC treatment</p> <p>One patient had euphoria and lightheadedness</p>	—
Epilepsy Devinsky et al, ¹² 2017	Fourteen-wk treatment; 15% discontinued treatment before 14 wks	CBD titrated up to 20 mg/kg per d in twice-daily dosing over 2 wks	Median monthly convulsive seizures decreased from 12.4 to 5.9, as compared with 14.9 to 14.1 with a placebo ($P = .01$), for an adjusted median seizure reduction of 22.9% with CBD compared with a placebo	<p>Somnolence (36%), diarrhea (31%), decreased appetite (29%), and vomiting (15%)</p>	Median frequency of total seizures (all seizure types) decreased 28.6% with CBD compared with 9.0% with a placebo ($P = .03$)
Gofshteyn et al, ¹³ 2017	Acute treatment after status epilepticus ($n = 2$) Median 91 d for chronic treatment (range 3–87 mo)	CBD titrated up to 25 mg/kg per d Final dose ranged from 15 to 25 mg/kg per d	Marked reduction in seizure frequency and duration in 86% of patients During chronic treatment, seizure frequency reduced by 91% at 4 wks and 65% at 48 wks	<p>Drowsiness (29%) and decreased appetite with weight loss ($n = 1$)</p>	With addition of CBD, mean adjunct AEDs reduced from 7.1 to 2.8
Kaplan et al, ¹⁴ 2017	Mean 48.6 wk of treatment (range 6–82)	CBD titrated from 2 mg/kg per d in twice-daily dosing to a maximum of 25 mg/kg per d. Final dose ranged from 5 to 25 mg/kg per d	Seizure frequency decreased in 4 of 5 subjects by 14 wks and most recent visit	<p>Temporary increased seizures ($n = 5$) and behavioral issues ($n = 2$)</p>	Improved quality of life, with subjective fine motor and cognitive improvements ($n = 3$)
Treat et al, ¹⁵ 2017	Mean 11.7 mo of treatment (range 0.3–57)	OCE	Seizures improved in 49% of patients, with 24% considered responders (>50% reduction in seizure burden) Higher response with LGS (58%) compared others ($P < .05$)	<p>Worsening seizures (10%), somnolence (6%), and GI symptoms (5%)</p> <p>Nineteen percent reported an adverse event</p>	Seventy-one percent discontinued OCE use during the study period
		Cannabinoid ratios and dose information infrequently documented and not analyzed			

TABLE 3 Continued

Study by Indication Authors, y	Duration of Treatment and Follow-up	Medication Dosing, Frequency, and Formulation	Primary and Secondary Outcomes	Side Effects	Additional Clinical Findings
Devinsky et al, ¹⁶ 2016	Twelve-wk treatment; 7% discontinued treatment before 12 wks	CBD titrated from 2–5 mg/kg per d up to 50 mg/kg per d	Total seizures decreased by median of 35% ($P < .05$)	Somnolence (25%), diarrhea (19%), decreased appetite (19%), and fatigue (13%)	Concurrent clobazam use associated with a 50% reduction in motor seizures ($P = .01$)
		Mean CBD dose was 22.7 mg/kg per d in efficacy analysis group and 22.9 mg/kg per d in safety analysis group	Monthly motor seizures decreased by median of 37%, from a baseline of 30 to 16 monthly motor seizures	Six percent had treatment-emergent status epilepticus	Greatest seizure reduction in patients with focal seizures (median 55% decrease) and atonic seizures (54%), followed by tonic seizures (37%) and tonic-clonic seizures (16%)
		Median 3 daily doses (range 1–7)	Thirty-seven percent of patients had at least a 50% reduction in seizures, 22% had at least a 70% reduction, and 8% had a 9% reduction	Three percent discontinued treatment because of adverse events	
		Ninety-nine percent pure oil-based CBD extract dissolved in sesame oil-based solution			
Tzadok et al, ¹⁷ 2016	Median 5.5 mo of treatment (range 3–12), with median 10 mo follow-up	CBD-enriched OCE, with CBD dose of 1–20 mg/kg per d, titrated by seizure response and side effects	Reduced seizures in 89% of patients	Seven percent of patients reported worsening seizures leading to discontinuation	—
		CBD to THC ratio of 20:1	Eighteen percent of patients had a 75%–100% reduction, 34% had a 50%–75% reduction, 12% had a 25%–50% reduction, and 26% had a <25% reduction		
		Canola oil-based solution			
Hussain et al, ¹⁸ 2015	Median 6.8 mo of CBD treatment	CBD-enriched OCE, with at least 15:1 CBD-to-THC ratio	Reduced seizures in 85% of patients	Increased appetite (30% vs 13%; $P = .002$) and weight gain (29% vs 18%, $P = .08$) compared with pretreatment	Median 2 AEDs adjunct to CBD
		Median reported CBD dose of 4.3 mg/kg per d, administered 2–3 times daily	Fourteen percent reported seizure freedom		
Press et al, ¹⁹ 2015	Mean follow-up of 5.6 mo (range 1–24)	OCE with 70% reporting CBD only and 11% reporting CBD only with other OCE	Reduced seizures in 57% of patients	Increased seizures (13%), somnolence and/or fatigue (12%), and GI symptoms (11%)	Fifteen percent of patients discontinued use, of which 91% had treatment response
		Dosing information infrequently documented and not analyzed	Thirty-three percent considered treatment responders, with >50% reduction in seizures		
			Response greater in LGS compared with Dravet and Doose syndromes ($P < .05$)		
Saade and Joshi, ²⁰ 2015	6 mo of treatment	CBD titrated from 10 to 25 mg/kg per d over 15 d, divided twice daily	Seizure frequency decreased from 10–20 per d to 5 per wk, with up to 9 d of clinical seizure freedom	None observed	—
Porter and Jacobson, ²¹ 2013	Treatment ranged from 2 wks to >1 y	CBD-enriched OCE	Reduced seizures in 84% of patients.		
		CBD content ranged from <0.5 to 28.6 mg/kg per d.	Forty-two percent reported a >80% seizure frequency reduction, 32% reported a 25%–60% reduction, and 11% reported seizure freedom		
		THC dose ranged from 0 to 0.8 mg/kg per d			

TABLE 3 Continued

Study by Indication Authors, y	Duration of Treatment and Follow-up	Medication Dosing, Frequency, and Formulation	Primary and Secondary Outcomes	Side Effects	Additional Clinical Findings
Lorenz, ²² 2004	—	Dronabinol mean dose of 0.07 mg/kg per d	Reduced seizures in 2 of 6 patients One had stable seizure burden despite NCL progression	Both patients who responded had a temporary increase in seizure severity One had increased sensitivity to aversive smells	One patient had no observed changes, 1 could not be evaluated because of NCL progression, and 1 could not be evaluated because of AED changes
Neuropathic pain Rudich et al, ²³ 2003	12 mo treatment with weekly follow-up	Dronabinol oral capsule started at 5 mg QHS, titrated in 5 mg increments, to maximum of 20 and 25 mg daily	At 4 mo, 40% and 60% reduction in the affective component of pain, and functional improvements in sleep (50% and 100%), ADL (60% and 75%), mood (75% and 100%), and academics (10% and 100%) One patient reported a 45% reduction in voiding pain	Increased appetite, morning sleepiness, lightheadedness, and dysphoria, all of which subsided with slower titration or lower dose	Efficacy declined after 6–12 mo, resulting in discontinuation
PTSD Shannon and Opila-Lehman, ²⁴ 2016	5 mo of treatment	CBD 25 mg Q6PM, with 6–12 mg QD PRN anxiety	Decreased anxiety with SCARED score reduced from 34 to 18 Improved sleep with SDCS score reduced from 59 to 38	None observed	—
Spasticity Kuhlen et al, ²⁵ 2016	Median 181 d of treatment (range 23–1429)	Dronabinol 2.5% solution BID, titrated from 0.83 mg BID to 0.08–1.0 mg/kg per d (median 0.33 mg/kg per d)	Clinician-documented spasticity reduced in 75% of patients	Restlessness (<i>n</i> = 1), mood deterioration (<i>n</i> = 1), and vomiting (<i>n</i> = 1) One patient discontinued treatment because of restlessness and a lack of efficacy None reported	No habituation effect noted in responders Response in 13% of patients could not be objectively determined
Lorenz, ²⁶ 2002	—	Dronabinol 0.07 mg/kg per d, dispensed in 2.5% oil drops, divided twice daily	Reduced spasticity within a few days	None reported	—
Tourette syndrome Hasan et al, ²⁷ 2010	9 wks	Δ-9-THC titrated from 5 mg QAM to 15 mg daily	YGTSS score decreased from 97 to 54 and GTS-QoL score decreased from 54 to 21 at 7 wk TMS measures of intracortical inhibition increased	Transient mild euphoria (<i>n</i> = 1)	Minimal decrease of ADHD symptoms before the addition of methylphenidate

ADHD, attention-deficit/hyperactivity disorder; ADL, activities of daily living; AED, antiepileptic drug; BID, twice daily; BSA, body surface area; GI, gastrointestinal; GTS-QoL, Gilles de la Tourette Syndrome–Quality of Life Scale; LGS, Lennox-Gastaut syndrome; NCL, neuronal ceroid lipofuscinosis; OCE, oral cannabis extract; PRN, as needed; Q6H, every 6 hours; Q6PM, every night at 6 PM; QD, once daily; QHS, every night; SCARED, Screen for Child Anxiety Related Disorders; SDCS, Sleep Disturbance Scale for Children; TID, 3 times daily; TMS, transcranial magnetic stimulation; YGTSS, Yale Global Tic Severity Scale; —, not applicable.

conducted a retrospective chart review of 74 children and adolescents with treatment-resistant epilepsy and reported that CBD-enriched medical cannabis reduced seizures in 89% of patients.

In a small survey of 19 parents of children with treatment-resistant epilepsy, Porter and Jacobson²¹ found that CBD-enriched cannabis reduced seizure frequency in 84% of patients. In a follow-up on this early report, Hussain et al¹⁸ further surveyed 117 parents of children with epilepsy and found that CBD-enriched cannabis reduced seizures in 85% of patients. In a case series of 6 children with epilepsy, Lorenz²² reported that dronabinol reduced seizures in 2 of the patients. Saade and Joshi²⁰ reported that CBD reduced seizure frequency in a 10-month-old patient with malignant migrating partial seizures of infancy.

Medical Cannabinoids for Spasticity

In a retrospective chart review of 12 children, Kuhlen et al²⁵ described the effects of dronabinol for treatment-refractory spasticity related to developmental disorders at a palliative care setting. Dronabinol solution given twice daily reduced spasticity and was continued for a median of 181 days with no habituation observed. In a case report, Lorenz²⁶ reported that dronabinol reduced spasticity and myoclonus in a toddler with a neurodegenerative disease called neuronal ceroid lipofuscinosis.

Medical Cannabinoids for Other Indications

In a case report of 2 adolescents with neuropathic pain and comorbid major depressive disorder, Rudich et al²³ reported that dronabinol reduced the affective component of pain by 40% and improved psychosocial functioning after 4 months, although there was a gradual dissipation of effectiveness after 6 months that led to discontinuation.

Shannon and Opila-Lehman²⁴ reported that CBD improved anxiety and sleep in a case report of a 10-year-old girl with PTSD from early childhood trauma. Hasan et al²⁷ reported that δ -9-THC decreased tic severity and improved quality of life in a case report of a 16-year-old patient with treatment-refractory Tourette syndrome.

DISCUSSION

This systematic review based on PRISMA guidelines identified 22 studies that evaluated the therapeutic benefits of medical cannabinoids in 795 children and adolescents, although 2 sets of studies (ie, 2 retrospective chart reviews and 2 parent surveys) may have had overlap in their sample groups. The study methods were heterogeneous, with only a minority of studies designed and powered for efficacy analysis (6 of 22). Of the double-blind RCTs ($n = 5$), all reported statistically significant postintervention reductions in the primary outcomes of CINV ($n = 4$) and convulsive seizures ($n = 1$). An open-label trial for treatment-refractory epilepsy also reported statistically and clinically significant postintervention reductions in seizure frequency, although the lack of a blinded control group limits the strength of the conclusion. Although the remaining reports suggested that cannabinoids were associated with improvements in CINV ($n = 2$), seizures ($n = 9$), spasticity ($n = 2$), tics ($n = 1$), PTSD ($n = 1$), and neuropathic pain ($n = 1$), the publications were not designed to evaluate the statistical significance of outcomes. In comparison with the paucity of pediatric studies on medical cannabinoids, the adult literature is relatively more substantive. Therefore, to facilitate an interpretation of the findings of this review, the identified pediatric studies are interpreted in context of a larger adult literature.

CINV

Although several of the RCTs investigating CINV date back to the 1980s, there is quality evidence that cannabinoids are effective as an antiemetic in children undergoing chemotherapy. Of note, all 6 studies used a THC cannabinoid, including δ -8-THC, δ -9-THC, dronabinol, and nabilone. The studies demonstrate that THC is more efficacious than antiemetics such as prochlorperazine, metoclopramide, and domperidone, although side effects of drowsiness and dizziness were common. This evidence parallels the adult literature. In a Cochrane review of 23 adult trials, Smith et al²⁸ reported that cannabinoids are more efficacious than a placebo and are similar to conventional antiemetics in the treatment of CINV.

Epilepsy

The research in cannabinoids as a seizure treatment in children has grown rapidly over the past decade, with the number of studies investigating it as an antiepileptic equaling the number of studies for all other pediatric conditions combined. The 11 studies suggest cannabinoids may have a therapeutic benefit for seizures from different etiologies, including treatment-refractory epilepsy as studied in 8 of the studies. CBD is the cannabinoid that appears to have more evidence for efficacy as used in 8 of the 11 studies, including the only RCT and all 3 prospective open-label studies. However, most studies lacked a placebo control group, and the resulting potential for regression to the mean greatly reduces the strength of conclusions. Furthermore, the 2 survey studies recruited parents from online forums and a parent interest group, both of which are at high risk of sampling bias. In contrast to other diagnoses, the pediatric literature on cannabinoids for epilepsy informs the adult literature in this area, not vice versa.

Spasticity

Researchers in 2 studies, which are at high risk of bias because of a lack of controls and blinding, examined dronabinol for the treatment of spasticity in children with developmental disabilities. This evidence, albeit limited, parallels the adult literature. In summarizing 2 systematic reviews and an additional RCT of adult patients, the National Academy of Sciences²⁹ concluded there was substantial evidence that oral cannabinoids benefit patient-reported spasticity symptoms, although the evidence is primarily from populations with multiple sclerosis. Nabiximols, an oromucosal spray containing an ~1:1 ratio of THC to CBD, is a medication approved in Canada and multiple European countries for the treatment of adult patients with spasticity from multiple sclerosis and remains in phase 3 of FDA trials in the United States.

Neuropathic Pain

Researchers in only 1 case report of 2 adolescents that lacked controls and blinding examined dronabinol for treatment of neuropathic pain; therefore, conclusions are limited. However, these preliminary findings tentatively align with findings in the adult literature. A systematic review by Whiting et al³⁰ identified 28 RCTs of adults with chronic pain, of which 17 trials were related to a neuropathy; the resulting analysis suggested that cannabinoids lead to greater improvement in pain. In addition, Andreae et al³¹ conducted a subsequent systematic review of inhaled cannabis for peripheral neuropathy, which demonstrated pain relief with a possible dose-dependent effect.

PTSD

Researchers in only 1 case report at high risk of bias given a lack of controls and blinding have examined

CBD for the treatment of PTSD; therefore, conclusions are also limited. The limited adult literature is conflicting in regard to the association between cannabinoids and PTSD. In the only RCT, Jetly et al³² reported that nabilone improved nightmares, global clinical state, and general well-being compared with a placebo in a crossover design. However, this single study contrasts with nonrandomized literature that shows limited evidence of an association between cannabis use and increased PTSD symptom severity.^{31,33}

Tourette Syndrome

Researchers in only 1 case report at high risk of bias given a lack of controls and blinding investigated the benefits of δ -9-THC in Tourette syndrome. In this case study, THC was associated with a reduction in tic severity. In the adult literature, 2 small controlled trials suggested a benefit of THC on tic severity in Tourette syndrome, although the reports are at similarly high risk of bias given the lack of an adequate description of randomization, allocation concealment, and incomplete outcome data.^{34,35}

Limitations

The literature on medical cannabinoids in children and adolescents is constrained by several important limitations, including between-study heterogeneity in the studied cannabinoid form and dosage (ie, CBD and THC content), indication, and ages of the sample. The sample sizes in many studies were small, with 13 of the 22 studies containing <20 participants. Notably, 17 of the 22 studies lacked a control group, and 16 of the 22 studies were not designed to test the statistical significance of changes in outcome measures. Finally, most studies lacked long-term follow-up to test for potential adverse neurocognitive and psychiatric side effects that have

been demonstrated in recreational cannabis studies.

Risks of Cannabinoids

Although there is evidence for potential benefits in pediatric populations, pediatricians, families, and patients must balance the decision to use medical cannabinoids with the associated risks. In controlled trials, THC most commonly led to side effects of drowsiness and dizziness, with severity associated with higher doses. However, no major side effects were reported with dose reduction. The most common side effects with CBD were somnolence, diarrhea, and decreased appetite. In the controlled trial, although 75% of patients receiving CBD experienced side effects, only 13% withdrew from the trial because of the side effects. This parallels a systematic review of adult side effects from medical cannabinoids, which found dizziness and somnolence as the most commonly reported adverse events, followed by muscle spasm, pain, and dry mouth; notably, there was no evidence of a higher incidence of serious adverse events.³⁶ Of note, accidental overdose of cannabis has been associated with multiple adverse effects, including reports of seizures among toddlers, which may be because of the toxicity of high-dose THC.³⁷

The paucity of the studies limits our understanding of long-term risks associated with medical cannabinoids in pediatric populations. In the absence of substantive quality data from literature on medical cannabinoids, we highlight the findings of harms from recreational cannabis literature. There are important differences between recreational and medical cannabinoid use, including frequency, dosing, and potency, as well as significant confounds in the recreational use population, such as comorbid substance use and psychiatric

illness. Although the applicability of the findings from the recreational cannabis literature to medical cannabinoids remains uncertain, pediatricians and families should understand the potential risks because it directly informs the decision for medical cannabinoid treatment.

The brain, including the endocannabinoid system, undergoes active development during adolescence,³⁸ which may confer increased vulnerability to adverse long-term outcomes from cannabinoid use before adulthood. Cannabinoid receptors type 1 are particularly concentrated in brain regions that are critical for executive functioning, reward processing, and memory, including the prefrontal cortex, anterior cingulate cortex, basal ganglia, hippocampus, amygdala, and cerebellum.³⁹ Neuroimaging studies show that individuals who begin using cannabis regularly in adolescence tend to have differences in cortical and subcortical volumes, white matter integrity, and functional connectivity compared with nonusers.⁴⁰ The structural and functional neuroimaging differences appeared to correlate with cognitive impairments, such as attention deficits associated with right-hippocampus activation,⁴¹ verbal memory deficits associated with frontoparietal circuitry,⁴² and poorer executive functioning associated with prefrontal cortex volume.⁴³

In a large, prospective study, long-term cannabis use in adolescents was associated with lower-than-expected IQ scores at follow-up,⁴⁴ although this finding is confounded by familial environment, genetic liability, and sociodemographic factors, such as school dropout.^{45,46} Studies have demonstrated a dose-response relationship between cannabis use (ie, frequency, quantity, and duration) and cognitive impairments, including deficits in verbal learning

and memory,⁴⁷ psychomotor performance,⁴⁸ and attention.⁴⁹ Converging lines of evidence showed that the onset of cannabis use before age 16 years, compared with later onset, is associated with poorer attention,⁵⁰ executive functioning,⁵¹ memory performance,⁴⁷ and verbal IQ.⁵²

Notably, recreational cannabis users in controlled settings have shown a preference for certain types of medical cannabinoids, including dronabinol and high-dose nabiximol, in comparison with a placebo, suggesting an abuse liability in at-risk populations.⁵³ Long-term recreational use of cannabis is associated with risk of cannabis use disorder, which is characterized by impaired control over cannabis use and difficulty in ceasing use despite its harms. An estimated 8.9% of cannabis users escalate use to meet cannabis use disorder criteria.⁵⁴ For those who initiate use in adolescence, the risk of cannabis use disorder rises to 1 in 6,⁵⁵ with peak risk appearing at ~17 years of age.⁵⁶ Furthermore, twin studies reported that adolescent cannabis users have an elevated risk of developing other substance use disorders.⁵⁷

One study has reported that recreational, frequent cannabis use during adolescence before age 15 years has been associated with an increased risk of depression.⁵⁸ However, subsequent longitudinal studies reported contradicting results,⁵⁹ with baseline depression associated with future initiation of cannabis use and suggesting confounds, such as sociodemographic factors and comorbidities, that limit conclusions regarding simple causality. Twin studies showed early-onset cannabis use and depression likely reflect shared genetic and environmental vulnerabilities.⁶⁰ Adolescent cannabis use, particularly earlier onset and regular use, has also been associated with later suicidality.^{60,61}

Cannabis use in early adolescence is further linked to earlier onset of psychotic disorders among at-risk populations.⁶² Adolescents who use cannabis regularly subsequently reported higher levels of subclinical psychotic symptoms, such as paranoia and hallucinations, and the effect persisted despite 1 year of abstinence.⁶³

A review of prospective longitudinal studies reported that early cannabis use increases risk of poor school performance, particularly leaving school early.⁶⁴ Adolescent cannabis use is also linked to externalizing problems, such as delinquent and aggressive behavior.⁶⁵ Finally, increasing levels of cannabis use before age 21 years was associated with higher unemployment and welfare dependence and lower levels of income and relationship and life satisfaction by age 25 years.⁶⁶

CONCLUSIONS

This review raises an important methodological issue in the field. Although we found a larger number ($n = 2743$) of citations that invoked terms related to cannabinoids in children and adolescents, we identified only 22 studies that examined cannabinoids for clinical indications in the pediatric population. Under the Controlled Substances Act of 1970, cannabis remains a Schedule I drug, and restrictive regulations continue to limit the research of medical cannabinoids. Concurrently, medical cannabinoids are becoming increasingly available to populations because of state legalization, of which cannabis plant products that are available in dispensaries may have highly variable cannabinoid concentrations. Finally, potential neurocognitive and psychiatric harms have been identified in the recreational cannabis literature. In this context, pediatricians,

families, patients, and policy makers continue to lack urgently needed information to make balanced decisions regarding the use of medical cannabinoids in children and adolescents.

In summary, the objective of this systematic review was to synthesize the current state of the research on medical cannabinoids in children and adolescents. Beyond studies of CINV and epilepsy, the findings provided limited evidence of variable quality supporting the

use of cannabinoids for different clinical indications. Additional larger, prospective, and controlled studies are required to better delineate the medical utility of cannabinoids in different pediatric disorders. This body of evidence has important implications in identifying the risks and benefits of medical cannabinoids in children and adolescents, especially in the context of psychiatric and neurocognitive adverse effects that have been identified from pediatric studies of recreational cannabis use.

ABBREVIATIONS

CBD: cannabidiol
CINV: chemotherapy-induced nausea and vomiting
FDA: Food and Drug Administration
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
THC: tetrahydrocannabinol

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Medical Cannabinoids in Children and Adolescents: A Systematic Review

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