Medical Cannabis and Cannabinoids

Review Article

Med Cannabis Cannabinoids 2024;7:257–267
DOI: 10.1159/000542550

Received: January 17, 2024
Accepted: November 4, 2024
Published online: December 10, 2024

Use of Cannabis-Based Medical Products for Pediatric Health Conditions: A Systematic Review of the Recent Literature

Mitchell L. Doucette[a] Dipak Hemraj[a] David J. Casarett[b] D. Luke Macfarlan[a] Emily Fisher[a]

[a]Health Economics and Outcomes Research Division, Leafwell, Miami, FL, USA; [b]Department of Medicine, Duke University, Durham, NC, USA

Keywords
Medical cannabis · Pediatrics · Efficacy · Literature review

Abstract

Introduction: Cannabis policy is rapidly changing in the USA and across the globe, with 24 states legalizing cannabis for adult use and 38 states making medical cannabis available for those with qualified conditions. Building on prior evidence, we reviewed the recently published literature (from the past 5 years) focused on the treatment effects of naturally derived medical cannabis products within the pediatric population. ***Methods:*** We conducted a systematic literature review of three electronic databases using MeSH terms and free-text. A study was eligible for inclusion if it investigated the efficacy of medical cannabis for any condition, it was published in 2019 or later, and the mean age of participants was under 21. We excluded studies that tested the effect of pharmaceutical cannabis-derived drug products. ***Results:*** We identified a total of 10 studies that met our inclusion/exclusion criteria. Of the 10, 2 utilized a double-arm randomized control trial (RCT) design, 3 used a single-arm trial design, and the remaining were observational studies, a case series, or a qualitative design. Aside from autism spectrum disorder (ASD) (n = 4), studies focused on cancer, treatment-resistant epilepsy, and Sturge-Weber syndrome (SWS). Four of the five single- or double-arm trials used a CBD:THC compound in a specific ratio as treatment. Both RCTs found significant improvement in ASD-related validated measures. Other studies found general improvements in validated measures of efficacy for SWS and epilepsy. Minimal adverse events were reported. ***Conclusion:*** In the pediatric population, emerging evidence, combined with existing literature, suggests medical cannabis may be beneficial for quality-of-life symptoms related to specific conditions, like cancer, ASD, treatment-resistant epilepsy, and SWS. More clinical trial data are necessary to establish medical cannabis as an addition to established medical guidelines.

Introduction

Cannabis policy in the USA and the world is rapidly changing [1]. Access to medical cannabis has increased and so have patients' and families' willingness to use cannabis as a medical treatment [2–8]. In recent years, research has increasingly focused on evaluating the relationship between medical cannabis and various conditions in the pediatric population, such as epilepsy [2, 9–12], palliative care [13, 14], autism spectrum disorder

karger@karger.com
www.karger.com/mca

Correspondence to:
Mitchell L. Doucette, mdoucette@leafwell.com

(ASD) [15–20], pain management [21], the gastrointestinal tract [22], and other conditions.

Cannabis, also known as marijuana, is a complex plant with over 100 compounds [23, 24]. Cannabis is a naturally occurring plant processed into various products for consumption. The plant contains many substances including terpenes that affect smell, flavonoids that affect flavor, and over 100 different phytocannabinoids [24]. There is no standardized form of cannabis, and each plant contains variable amounts of these substances. Medical cannabis can be administered through various methods, including smoking, vaporizing, oral tinctures or solutions, edibles, or topical applications such as patches or lotions. We refer to these as cannabis-based medical products.

Phytocannabinoids, or plant-derived cannabinoids, include delta-9 tetrahydrocannabinol (THC), known as the psychoactive component, and cannabidiol (CBD). These are the most widely used and studied components of cannabis. These elements interact with endocannabinoids and cannabinoid receptors distributed across the brain and spinal cord [25]. The receptors, part of the endocannabinoid system, play a regulatory role in various physiological processes. These include immune and cardiovascular functions, development of the nervous system, pain, inflammation, appetite regulation, among other functions [23–25].

Cannabis-derived drug products are also used for medical purposes. These products are either synthetic or plant-derived and are manufactured to treat various medical conditions. Major drug products include synthetic delta-9 THC products like dronabinol (brand names Marinol and Syndros) and nabilone (brand name Cesamet). Plant-derived products include nabiximols (brand name Sativex) and CBD (brand name Epidiolex), a CBD-based product.

In the USA, 38 states and the District of Columbia have legalized cannabis for both adult and/or medical use [26]. All states where cannabis is medically available have developed a medical cannabis program administered at the state level. In most states with operational medical cannabis programs, patients are required to obtain a medical card allowing them to purchase cannabis-based medical products. Medical cannabis use by a minor is permitted but necessitates consent from a legal guardian and certification from a physician.[1] Notably, registering with a medical cannabis program does not entitle patients to a prescription of FDA-approved drug products; only cannabis-based medical products are sold at dispensaries. The number of registered medical cannabis patients in the USA, including those under the age of 18, has grown in the past decade [27–31].

While the past decade has seen increases in state-level medical cannabis program registrations within the USA [29, 30], other countries with analogous medical programs have not experienced the same growth. In the UK, although medical cannabis is legal, patients encounter significant challenges in accessing products [32, 33], and thus, enrollment and usage have remained low. Canada, which has one of the oldest medical cannabis programs (beginning in 2001), is believed to have experienced increases in self-medication associated with the 2018 legalization of cannabis [34]. Challenges related to access and program complexity likely hinder registration in the Canadian medical cannabis program [34], and limited data reporting restricts research on pediatric medical cannabis use [7].

There have been two literature reviews published since 2017 regarding the overall efficacy and safety of medical cannabis in the pediatric population. Both of these reviews include cannabis-based medical products and cannabis-derived drug products as treatment arms. Wong and Wilens [35] published a systematic review of medical cannabis in children and adolescents. The authors did not focus on a specific disease state and identified 22 studies, of which five were randomized controlled trials. They found that the beneficial evidence was greatest for chemotherapy-induced nausea and vomiting, with some evidence also suggesting a benefit for pediatric patients with epilepsy. The authors noted insufficient evidence for muscle spasticity, neuropathic pain, post-traumatic stress disorder, and Tourette's syndrome [35]. Unsurprisingly, the majority of studies lacked control groups and were limited by small sample sizes.

Pawliuk and colleagues [3] published a scoping review examining the effect of medical cannabis in the pediatric population, citing the fast-evolving literature and building on Wong and Wilens' [35] work. The authors used multiple databases and the gray literature to identify articles that met their inclusion criteria, finding 36 studies. Of the 36 studies, 32 (88%) focused on accessing the efficacy or safety of medical cannabis in treatment-resistant (TR) epilepsy. The remaining 12% (n = 4) focused on various conditions, including studies related to pediatric cancer. Although the study's primary finding indicated a lack of evidence supporting the efficacy and safety of medical cannabis in the pediatric population, they did find a strong signal that medicinal cannabis

[1] In some states, medical cannabis programs require two physicians to certify a pediatric patient, and some require certification from a pediatrician or a pediatric subspecialist.

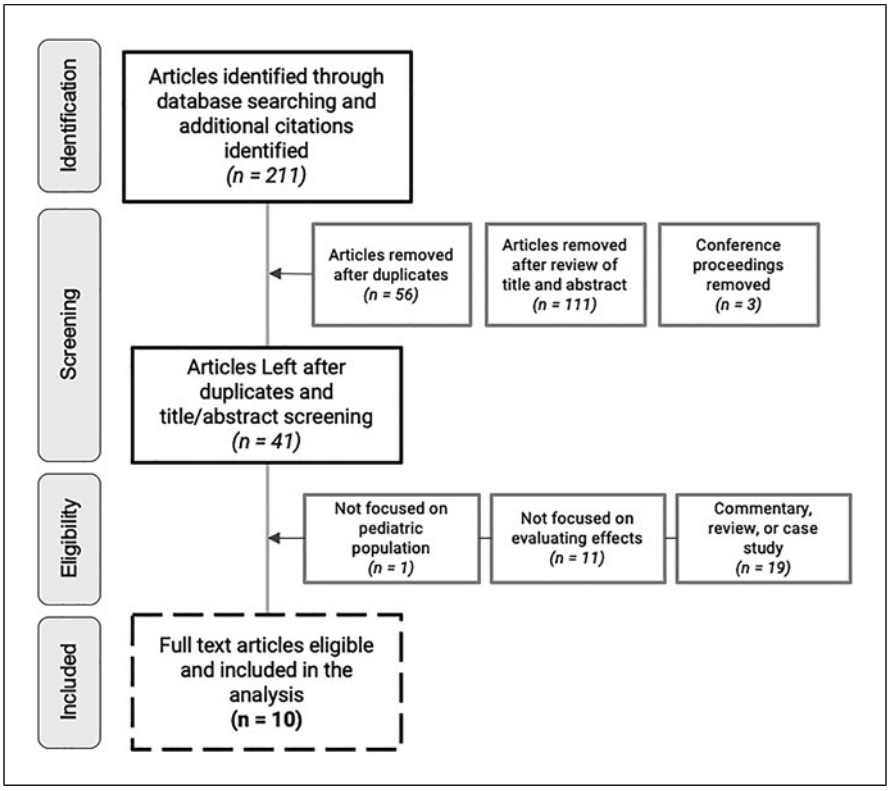

Fig. 1. Selection of studies retrieved for the literature review.

provided benefits for children with drug-resistant epilepsy and those with Dravet and Lennox-Gastaut syndromes [3]. However, they noted potential safety concerns, with treatment discontinuation due to adverse events ranging from less than 1–20%.

While Wong and Wilens [35] and Pawliuk and colleagues [3] provided timely reviews of medical cannabis treatment effects within the pediatric population, the former's literature review considered published articles until May 2017, while the latter's review considered articles published prior to 2019. In the intervening years, many more states have authorized or legalized cannabis, and additional literature has been published regarding the efficacy of medical cannabis in the pediatric population.

Thus, we aimed to contribute to this body of literature by reviewing recent studies on the efficacy and safety of cannabis-based medical products in the pediatric population. In this review, we focused on cannabis-based medical products, excluding cannabis-derived drug products like Epidiolex and Sativex. We made this decision because an increasing number of medical cannabis patients are using non-FDA-approved flower-based products for their conditions [29, 36]. It is more probable, especially in the USA and Canada, that a pediatric patient uses cannabis-based medical products purchased at a dispensary due to the product's ubiquity rather than a government-approved drug product. Therefore, reviewing the current literature on the effects of cannabis-based medical products on pediatric patients is essential.

Methods

Search Sources and Strategies

We conducted a systematic literature review following methods recommended by the Cochrane Collaboration. We documented our process and results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Fig. 1). Table 1 details the databases, search terms, and results related to our literature searches. We used free-text terms and explored MeSH headings for the topics of medical cannabis, medical marijuana, synthetic cannabinoids, and pediatrics. We first developed our search strategy in PubMed and adapted our search terms for the following databases: EBSCO – Academic Search Ultimate and Web of Science. We restricted our searches to include only articles written in English and excluded studies published before 2019. We included studies published through September 30, 2023, the date on which all final

Table 1. Search strategy: database and search terms

Database	Search term	Articles found, *n*
PubMed	("Pediatrics" [Mesh]) AND ("Medical Marijuana" [Mesh])	4
PubMed	("Pediatrics" [Mesh]) AND Medical Marijuana	23
PubMed	("Pediatrics" [Mesh]) AND Medical Cannabis	27
PubMed	("Pediatrics" [Mesh]) AND ("Cannabinoids" [Mesh])	20
Academic Search Complete	(DE "MEDICAL marijuana") AND "pediatrics" AND therapeutics	39
Web of Science	"Medical Cannabis" (All Fields) and "Pediatrics" (All Fields)	16
Web of Science	"Medical Marijuana" (All Fields) and "Pediatrics" (All Fields)	29
Web of Science	"Cannabinoids" (All Fields) and "Pediatrics" (All Fields)	47
Additional Citation Review		6
Total		211

searchers were completed. We retrieved additional studies based on hand searches of reference sections from relevant articles.

Study Selection and Extraction

We established the following inclusion criteria for this literature review. Included articles needed to involve the use of cannabis or a synthetic cannabinoid as a treatment option within a pediatric population. Articles were not limited by the type of medical condition being treated, nor were they limited by the methodology used. Additionally, we included review articles and commentaries. We excluded articles that focused on cannabis-derived drug products, such as Epidiolex and Sativex, and synthetic cannabis-related drug products, such as Marinol, Syndros, and Cesamet. We included studies that used phytocannabinoids, either THC or CBD. We excluded any articles in which the mean age of participants was 21 years or older. We included studies published within the past 5 years (2019 and later).

We reviewed all titles and abstracts, extracting the full texts of potentially relevant articles. M.L.D. and D.H. independently reviewed each paper to determine if it met the predefined inclusion criteria. We excluded duplicate publications. M.L.D. and D.H. met to resolve disagreements and finalized the list of publications included in the review (Fig. 1). From this final list, M.L.D. and D.H. independently extracted intervention details, outcome measures, and other study characteristics, documenting them in a data extraction spreadsheet.

We provided several tables in the results section. First, we reported characteristics for all included studies, including study authors, year, sample characteristics (such as population and mean age), presence of a control group, cannabis dosage, and administration routes. Second, we presented the primary and secondary outcomes, notable findings, and adverse events reported for the placebo-controlled and single-arm trials. We chose to provide this information only for placebo-controlled and single-arm trials as these designs incorporate temporality, making their reported outcomes and adverse events more robust from an inference perspective.

Results

From the 211 potential articles identified, 56 were excluded as duplicates, 111 were excluded based on title and/or abstract, and 3 were exlcuded as they were conference material (presentation/poster etc.) (Fig. 1). Among the remaining articles, 1 was excluded for not focusing on the pediatric population, 11 for not evaluating effects, and 19 for being commentaries, reviews, or a case studies (where $n = 1$). We included 10 full-text articles that met inclusion criteria for this analysis. Among the 10 studies, 1 was qualitative in nature. The study by Ananth and colleagues [37] was included as it uniquely captured qualitative effects of medical cannabis among pediatric cancer patients and their parents.

Characteristics of Included Studies

We examined various characteristics of the 10 included articles. All studies were published in 2019 or later. The types of studies included were three single-arm clinical trials [16, 17, 36], three observational studies [38–40], 1 case series [13], one qualitative interview study [37], and

Table 2. Summary of included articles evaluating medical cannabis treatment in pediatric populations

First author, published year	Article type	Sample, *n*	Country of origin	Primary type of cannabis	Control group (y/n)	Products used	Administration route	Mean age (median), years	Conditions
Ananth [37] (2021)	1:1 interview	15	USA	n/a	n/a	n/a	n/a	n/a	Cancer
Aran [41] (2021)	RCT[b]	150	Israel	CBD:THC	Yes	20:1 CBD:THC	Oral solution	11.8	ASD
Barchel [16] (2019)	Single-arm trial	53	Israel	CBD:THC	No	16 mg/kg CBD, 0.8 mg/kg (recommended)	Oral drops of oil	(11)	ASD
Bar-Lev Schleider [17] (2019)	Single-arm trial	188	Israel	CBD:THC	No	30% CBD, 1.5% THC, three times a day	Oil applied sublingually and dried flower	12.9	ASD
Divisic [13] (2021)	Case series	6	Italy	THC	No	Average 0.37 (mg/kg/day) effective dose	Oral solution	12	Palliative care
Erridge [38] (2023)	Observational	35	UK	CBD isolate, CBD broad spectrum, CBD:THC	No	Varied dosage	Varied usage	9.71	TR epilepsy
Silva [15] (2022)	RCT	60	Brazil	CBD:THC	Yes	9:1 CBD:THC with 0.5% mg/mL THC	Oral solution	7.7	ASD
Smegal [36] (2023)	Single-arm trial	10	USA	CBD	No	5–20 mg/kg/day	Oral solution	13.4[a]	SWS
Vaillancourt [39] (2020)	Observational	37	Canada	CBD:THC	No	Varied dosage	Varied usage	11.9	All
Zürcher [40] (2022)	Observational	90	Switzerland	CBD, CBD: THC, THC	No	Varied dosage	Varied usage	11.5	All

RCT, randomized control trial; ASD, autism spectrum disorder; TR epilepsy, treatment-resistant epilepsy; CBD, cannabidiol; THC, tetrahydrocannabinol; SWS, Sturge-Weber syndrome. Both RCT trials were placebo-controlled and double-blinded. [a]While the average age for this study was 13.4, there was a large range (3 years–34 years), 8 of the 10 included participants were under the age of 21. [b]In the Aran (2021) study, authors tested two different extractions of CBD:THC. One was whole-plant extract of CBD and THC; the other was purified CBD and THC at the same ratios of 20:1 CBD:THC.

two randomized controlled trials (RCTs) [15, 41]. The studies represented a diverse range of populations, with 2 studies from the USA, 3 from Israel, and 1 each from Italy, Brazil, Canada, and Switzerland (Table 2). Mean age was reported in 7 of the 10 articles, ranging from 7.7 to 13.4 years. The median age was provided in two studies: 11 and 12 years old. The largest study had 188 participants [17], and the smallest had 6 participants [13]. Overall, the average study population size was 64.4.

The most frequently studied condition was ASD, with 4 studies examining the therapeutic effects of medical cannabis on ASD. Two observational studies did not focus on any specific type of illness and documented the effects of medical cannabis across a range of outcomes; one observational study examined the therapeutic effects on TR epilepsy. The case series examined the use of medical cannabis in the palliative care. Other conditions included pediatric cancer, TR epilepsy, and Sturge-Weber syndrome.

Treatment Dosage and Administration Routes

The primary treatment type used in the studies was some ratio compound of CBD:THC. Among the five single- or two-arm trials identified, four [15–17, 41] used a CBD:THC product and one used CBD only [36]. Aran and colleagues [41] used a 20:1 CBD:THC oral treatment, given sublingually whenever possible. Notably, the study was a 28-week cross-over design with a 4-week washout period and tested both a whole-plant extract and a purified extract, both with the same 20:1 ratio. Barchel and colleagues [16] used a 16 mg/kg: 0.8 mg/kg ratio of CBD:THC oral solution as treatment. Bar-Lev Schleider and colleagues [17] used a 30% CBD to 1.5% THC oil, applied under the tongue and dried flower. Silva and colleagues [15] used a 9:1 CBD:THC oral solution where THC was restricted to 0.5 mg/mL as treatment. Smegal and colleagues [36] used an oral solution that escalated over the study period, beginning at 5 mg/kg/day CBD and increasing up to 20 mg/kg/day as tolerated. Fifty percent of the study participants reached 20 mg/kg/day. Divisic and colleagues' study [13], which was a 6-person case series, was the only study to test THC only. In this study, the average dosage was 0.37 mg/kg/day, administered in oil.

The observational studies documented various types of medical cannabis treatments used during their study periods. As these studies were not controlled trials, the dosage and treatment types varied. Erridge and colleagues [38] used data from the UK Medical Cannabis Registry to identify those with drug-resistant epilepsy. Of the 35 pediatric cases, 19 received a CBD isolate, and 17 received a broad-spectrum CBD or a CBD combination therapy (not mutually exclusive). In Vaillancourt and colleagues [39] conducted a retrospective chart review study using data from the Children's Hospital of Eastern Ontario from 2014 to 2017. The authors found that treatment type information was not always available, but for cases with data, a CBD:THC ratio product was used in various forms. Zürcher and colleagues [40] analyzed medical data from one pharmacy in Switzerland (one of only two pharmacies eligible to provide medical cannabis in the country at the time). The study found CBD, CBD:THC, and THC treatments with varying dosages and administration routes.

Findings and Adverse Events

Table 3 provides primary and secondary reported outcomes (if noted), along with notable findings and information on adverse events from the five included trials. Two trials (Aran, 2021, and Silva, 2022) used a placebo-controlled, double-blinded RCT study design. Both studies evaluated the impact of a CBD:THC medical cannabis treatment on ASD, with one in Israel and one in Brazil.

Aran and colleagues [41] found that 49% of respondents in the whole-plant extract arm reported being either "much improved" or "very much improved" on the Clinical Global Impression-Improvement Scale (CGI-I), a primary outcome measure (p value = 0.005). The CGI-I is a validated measure assessing a patient's global function before and after the initiation of medication [42, 43]. They did not find any significant change in their other primary outcome, scores from the Home Situation Questionnaire-Autism Spectrum Disorder (HSQ-ASD) [44]. As this study was a 28-week cross-over trial with a 4-week washout period, the authors only evaluated the first 12-week period due to potential treatment order effects. The adverse events in this study were relatively mild, with 28% and 25% reporting somnolence and decreased appetite, respectively, while 8% and 15% of the placebo group also reported somnolence and decreased appetite.

Silva and colleagues [15] measured the impact of medical cannabis over a 12-week period. The study team used semi-structured interviews to assess a variety of ASD-related symptoms. They also utilized the Autism Treatment Evaluation Checklist (ATEC), a diagnostic tool for evaluating treatment effectiveness in autistic patients [45], and the Childhood Autism Rating Scale (CARS), a rating scale used in autism detection and diagnosis in children [46]. The authors found that psychomotor agitation, meals, social interaction, and anxiety showed significantly lower scores in the treatment group compared to the placebo group (all p values <0.05).

Table 3. Summary of notably findings and adverse events for single- or double-arm trials

First author, published year	Primary reported outcomes	Secondary outcomes	Notable primary findings	Adverse events reported
Aran [41] (2021)	Home Situation Questions-ASD & Clinical Global Impression-Improvement Scale (CGI-I)	ADOS-2, VABS, CARS-2, APSI	CGI-I improved 49% (p value = 0.005), no change in HSQ-ASD	Somnolence (28%), decreased appetite (25%); placebo group reported 8% and 15%, respectively
Barchel [16] (2019)	Number of self-injury and rage attacks, sleep problems, anxiety[a]		Overall, 74.5% of patients reported improvement in symptoms, 11% reported no change, and 3.9% reported worsening	Adverse events were mild and included somnolence and change in appetite
Bar-Lev Schleider [17] (2019)	Quality-of-life[c]	Rage attacks, agitation, sleep problems, speech impairment, cognitive impairment, anxiety, incontinence, seizures, limited mobility, constipation, tics, digestion problems, increased appetite, lack of appetite, depression	There was a statistically significant increase in the percent of patients who reported good life quality at baseline compared to 6 months (31.3% compared to 66.8%, p value <0.001)	Of the sample, 25.2% reported at least on side effect included restlessness (6.6%), sleepiness (3.2%), psychoactive effects (3.2%) increase appetite (3.2%), digestion problems (3.2%), dry mouth (2.2%), and lack of appetite (2.2%)
Silva [15] (2022)	Aggressiveness, psychomotor agitation, concentration, meals, sleep, social interaction, verbal language, anxiety, repetitive and stereotyped movements, ATEC & CARS-2[b]		Study found improvements in all primary outcomes. Secondary outcomes did not show statistically significant changes	Of the treatment group, 9.7% of the patients reported adverse events including dizziness, insomnia, colic, and weight gain
Smegal [36] (2023)	SWS NeuroScore, quality-of-life, anxiety, emotional regulation, migraines, bimanual ability		All subjects showed improvements from SWS NeuroScores from baseline (p = 0.002). Seven of nine participants reported improvements to quality-of-life scores	Seven out of ten subjects reported adverse events including dizziness, headache, and decreased appetite

ADOS-2, Autism Diagnostic Observation Schedule; VABS, Vineland Adaptive Behavior Scales; CARS-2, Childhood Autism Rating Scale-Second Edition; APSI, Autism Parenting Stress Index; ATEC, Autism Treatment Evaluation Checklist; SWS, Sturge Weber syndrome. [a]Study did not note scales used to evaluate these conditions. Evaluations were made by parents and reported to study. As this was a case series, no statistical methods were used to assess this change. [b]Study used semi-structured interviews to assess primary outcomes. [c]Quality-of-life measures on a three-point Likert scale using the World Health Organization's Quality-of-Life Scale.

However, they did not find any significant changes to the ATEC subscales or the CARS scale. The number of adverse events was similar in the treatment group (n = 4) compared to the control group (n = 5), with only 3 subjects reporting 4 symptoms in the treatment group.

Other single-arm trials found general symptom improvements related to medical cannabis treatment with relatively mild adverse events. Barchel and colleagues [16] found general improvement in patient symptoms in their sample of 53 pediatric patients, with mild adverse events including somnolence and changes in appetite. Bar-Lev Schleider and colleagues [17] found statistically significant increases in quality-of-life scores compared with baseline to the 6-month follow-up. However, in this study

of 188 participants, 25% reported at least one adverse event, with the most common being restlessness (6.6%). Smegal and colleagues [36], in their study of 10 participants, found significant improvements in multiple outcomes, including patient-reported quality of life. The authors reported that the treatment was well tolerated, with mild to moderate side effects in 6 out of 10 patients. The three observational studies identified in this review also found results similar to the placebo-controlled or single-arm trials, indicating that medical cannabis produced measurable effects with relatively modest adverse events.

Results from the one qualitative study included, while not generalizable to the broader population, provide notable contextual information related to the use of medical cannabis in the pediatric population. Ananth and colleagues [37] conducted semi-structured interviews with 15 pediatric cancer patients and their parent(s) at a comprehensive cancer center in the USA. Findings of the study noted that parents were generally receptive toward using medical cannabis, often mentioning relief from nausea, anorexia, and pain related to chemotherapy or supportive care. Parents also expressed concerns about potential negative effects and the lack of comprehensive scientific literature, basing their decision to allow medical cannabis use on weighing both the benefits and risks A lack of trust in the medical system was evident as only a few participants consulted their oncologist about medical cannabis use, instead turning to other sources of information (e.g., internet, friends, peers).

Discussion

This systematic literature review identified 10 studies that evaluated the therapeutic efficacy and safety of medical cannabis in the pediatric population from 2019 onward. Specifically, we examined studies that focused on the effects of cannabis-based products and found generally positive effects across various disease states and populations. In total, the combined studies evaluated the effects of medical cannabis treatment in 644 children and adolescents. The studies included participants with mean ages ranging from 7.7 to 13.4 years across seven countries, utilizing various treatment products, dosages, and administration routes. The study methods were heterogeneous, with two placebo-controlled, double-blinded RCTs, three single-arm trials, three observational studies, one qualitative study, and one case series. Both RCTs reported notable improvements in ASD-related measures with mild to moderate adverse events.

Results from our review suggest that medical cannabis may be an emerging treatment complement when addressing ASD among the pediatric population. The studies with the strongest design (e.g., randomized controlled trials) both focused on ASD and found improvement in some primary outcomes related to medical cannabis treatment [15, 41]. Additionally, these two studies found no significant differences in other outcomes, suggesting that medical cannabis treatment did not worsen ASD-related health outcomes. In one single-arm trial by Barchel and colleagues [16], a small proportion of the ASD sample (3.9%) experienced worsening primary outcomes, while 74.5% reported improvement. In studies focused on ASD, the percentage of participants reporting adverse events ranged from 9.7% to 28%. Taken together, the strength of study designs, consistent findings, and relatively low adverse effect rates suggest that medical cannabis may contribute positively to patient treatment. However, there is large phenotypic variation across pediatric-aged ASD patients. Newer research ought to investigate whether there are specific ASD subtypes for whom medical cannabis may be more effective or less safe and which routes of administration are most effective.

Prior reviews of medical cannabis treatment in the pediatric population also found similar positive effects. Similar to the findings here, prior reviews noted that most published studies lacked a control group, were limited by small sample sizes, and varied in treatment dosages [3, 35]. Adverse events, such as somnolence and changes in appetite, were similarly frequent across previous reviews. Both prior reviews found the strongest evidence supporting medical cannabis use for conditions such as chemotherapy-induced nausea and vomiting. The current manuscript found the strongest evidence to be for ASD outcomes. The discrepancy in health condition findings may stem from this manuscript's exclusive focus on cannabis-based products. In contrast, previous reviews included cannabis-derived products, such as Epidiolex, which is specifically indicated for treating epilepsy. This is likely the primary reason for the discrepancy in the number of included studies between the 10 articles reviewed here and the 21 articles in Wong and Wilens [35] and 36 in Pawliuk and colleagues [3].

The products used in these studies typically contained a high concentration of CBD and a low concentration of THC. This is notable because individuals using medical cannabis through state-run programs in the USA or Canada may not have consistent access to similar high-CBD, low-THC products. Although the types of products available to medical cannabis patients vary by state, there

is a need for physicians to educate patients on the current literature.

The evidence presented here indicates a need for further research to fully comprehend the impact of medical cannabis treatment initiation on the pediatric population. Currently, conducting double-blind, placebo-controlled RCT studies with cannabis-based products (i.e., non-FDA-approved cannabis-derived products) faces multiple challenges. First, organizations encounter limitations due to the current FDA classification of cannabis as a Schedule I drug. Conducting studies with whole-plant cannabis or related products requires obtaining materials from the National Institute on Drug Abuse, with oversight from the Drug Enforcement Administration [47, 48]. Second, the market for medical cannabis producers is characterized by fragmentation and a lack of federal regulation. Unlike pharmaceutical companies, which are legally required to track adverse event data for their products, medical cannabis producers have no such obligation. Furthermore, there are little financial incentives for growers and retailers to conduct evidence-based research on the medical value of the products they cultivate and sell.

Other aspects of medical cannabis treatment, such as long-term use and drug-drug interactions, should also be considered. Little is known about the long-term safety profile of medical cannabis formulations in the general population and specifically in the pediatric population [49]. There is a potential for adverse neurodevelopmental effects with long-term use; therefore, the prescribing physician must consider each child's condition, prognosis, and risk profile [49]. Moreover, as THC and CBD are metabolized by CYP enzymes, there is a need for physicians to understand potential drug-drug interactions when prescribing medical cannabis [50]. In the USA, anxiety is one of the leading pediatric medical conditions treated with medical cannabis [51]. THC or CBD use may slow down the metabolism of antidepressants, resulting in adverse events.

One potential path forward for evaluating the therapeutic effects of flower-based medical cannabis is the use of real-world evidence [52, 53]. In lieu of regulated medical product markets, real-world evidence could help answer questions about effectiveness and safety [54]. Future research ought to use large-scale sources of real-world data to address these questions.

Limitations

This literature review on medical cannabis use in children and adolescents has limitations. The sample sizes in these studies were small to moderately sized, with most containing less than 100 participants. Notably, most studies lacked a control group or were observational studies. Some studies lacked long-term follow-up for potential adverse events. Furthermore, the products used in the included studies may not reflect the cannabis that is currently available on the retail medical cannabis market.

Conclusion

While more research is necessary, this review, together with other reviews of the literature [3, 35], suggests that medical cannabis is potentially a viable treatment option alongside established medical treatment guidelines. This is especially true for pediatric ASD.

Statement of Ethics

This research reviews publicly available manuscripts and does not involve human subjects.

Conflict of Interest Statement

M.L.D., D.H., E.F., and D.L.M. are employees of Leafwell and hold stock or stock options in Leafwell. Leafwell is a Telehealth company that connects potential medical cannabis patients to physicians in a friendly PC model and does not produce or sell cannabis products. No grant funding was used to sponsor this research. D.J.C. was a paid research consultant for Leafwell until November 2023.

Funding Sources

This research was not supported by funding.

Author Contributions

M.L.D. is the senior author, conceived ideas, led article curation and data analysis, and drafted the manuscript. D.H. contributed to writing and manuscript conception as well as data analysis. D.J.C. assisted with article conception and contributed to the final manuscript draft. E.F. and D.L.M. provided feedback through drafts and oversaw final manuscript products.

Data Availability Statement

All data/manuscripts analyzed for this literature review are publicly available.

References

1 Takakuwa KM, Schears RM. A history of the US medical cannabis movement and its importance to pediatricians: science versus politics in medicine's greatest catch-22. Clin Pediatr. 2019;58(14):1473–7. https://doi.org/10.1177/0009922819875550
2 Sobo EJ. Parent use of cannabis for intractable pediatric epilepsy: everyday empiricism and the boundaries of scientific medicine. Soc Sci Med. 2017;190:190–8. https://doi.org/10.1016/j.socscimed.2017.08.003
3 Pawliuk C, Chau B, Rassekh SR, McKellar T, Siden H. Efficacy and safety of paediatric medicinal cannabis use: a scoping review. Paediatr Child Health. 2021;26(4):228–33. https://doi.org/10.1093/pch/pxaa031
4 Hadland SE, Knight JR, Harris SK. Medical marijuana: review of the science and implications for developmental behavioral pediatric practice. J Dev Behav Pediatr. 2015;36(2):115–23. https://doi.org/10.1097/DBP.0000000000000129
5 Ebbert JO, Scharf EL, Hurt RT. Medical cannabis. Mayo Clin Proc. 2018;93(12):1842–7. https://doi.org/10.1016/j.mayocp.2018.09.005
6 Huntsman RJ, Elliott J, Lewis E, Moore-Hepburn C, Alcorn J, Mansell H, et al. Removing barriers to accessing medical cannabis for paediatric patients. Paediatr Child Health. 2024;29(1):12–6. https://doi.org/10.1093/pch/pxac129
7 Huntsman RJ, Kelly LE, Alcorn J, Appendino JP, Bélanger RE, Crooks B, et al. Improving the regulation of medical cannabis in Canada to better serve pediatric patients. CMAJ. 2021;193(41):E1596–9. https://doi.org/10.1503/cmaj.202169
8 Mansell H, Zaslawski Z, Mbabaali S, King PM, Kelly LE, Lougheed T, et al. Medical cannabis in schools: the experiences of caregivers. Paediatr Child Health. 2023;28(2):102–6. https://doi.org/10.1093/pch/pxac099
9 Ben-Zeev B. Medical cannabis for intractable epilepsy in childhood: a review. Rambam Maimonides Med J. 2020;11:e0004–8. https://doi.org/10.5041/RMMJ.10387
10 Talwar A, Estes E, Aparasu R, Reddy DS. Clinical efficacy and safety of cannabidiol for pediatric refractory epilepsy indications: a systematic review and meta-analysis. Exp Neurol. 2023;359:114238. https://doi.org/10.1016/j.expneurol.2022.114238
11 Hussain SA, Zhou R, Jacobson C, Weng J, Cheng E, Lay J, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox–Gastaut syndrome. Epilepsy Behav. 2015;47:138–41. https://doi.org/10.1016/j.yebeh.2015.04.009
12 Markle M, Nativio DG. Medical marijuana in the pediatric population with epilepsy – what you should know. J Pediatr Health Care. 2019;33(6):626–32. https://doi.org/10.1016/j.pedhc.2019.03.002
13 Divisic A, Avagnina I, De Tommasi V, Santini A, Brogelli L, Giacomelli L, et al. The use of medical cannabis in pediatric palliative care: a case series. Ital J Pediatr. 2021;47:229–10. https://doi.org/10.1186/s13052-021-01179-1
14 Oberoi S, Protudjer JLP, Rapoport A, Rassekh SR, Crooks B, Siden H, et al. Perspectives of pediatric oncologists and palliative care physicians on the therapeutic use of cannabis in children with cancer. Cancer Rep. 2022;5(9):e1551. https://doi.org/10.1002/cnr2.1551
15 Silva EA, Medeiros WMB, Torro N, Sousa JMM, Almeida IBCM, Costa FB, et al. Cannabis and cannabinoid use in autism spectrum disorder: a systematic review. Trends Psychiatry Psychother. 2022;44:e20200149. https://doi.org/10.47626/2237-6089-2020-0149
16 Barchel D, Stolar O, De-Haan T, Ziv-Baran T, Saban N, Fuchs DO, et al. Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and Co-morbidities. Front Pharmacol. 2019;9:1521. https://doi.org/10.3389/fphar.2018.01521
17 Bar-Lev Schleider L, Mechoulam R, Saban N, Meiri G, Novack V. Real life experience of medical cannabis treatment in autism: analysis of safety and efficacy. Sci Rep. 2019;9(1):200. https://doi.org/10.1038/s41598-018-37570-y
18 Fletcher S, Pawliuk C, Ip A, Oberlander T, Siden H. Symptoms, adverse events, and outcomes in the use of medicinal cannabis in children and adolescents with autism spectrum disorder: a scoping review protocol. JBI Evid Synth. 2021;19(5):1251–8. https://doi.org/10.11124/JBIES-20-00001
19 Fletcher S, Pawliuk C, Ip A, Huh L, Rassekh SR, Oberlander TF, et al. Medicinal cannabis in children and adolescents with autism spectrum disorder: a scoping review. Child Care Health Dev. 2022;48(1):33–44. https://doi.org/10.1111/cch.12909
20 Holdman R, Vigil D, Robinson K, Shah P, Contreras AE. Safety and efficacy of medical cannabis in autism spectrum disorder compared with commonly used medications. Cannabis Cannabinoid Res. 2022;7(4):451–63. https://doi.org/10.1089/can.2020.0154
21 Splinter W. Novel approaches for treating pain in children. Curr Oncol Rep. 2019;21(2):11. https://doi.org/10.1007/s11912-019-0766-6
22 Sunil M, Karimi P, Leong R, Zuniga-Villanueva G, Ratcliffe EM. Therapeutic effects of medicinal cannabinoids on the gastrointestinal system in pediatric patients: a systematic review. Cannabis Cannabinoid Res. 2022;7(6):769–76. https://doi.org/10.1089/can.2022.0192
23 Dharmapuri S, Miller K, Klein JD. Marijuana and the pediatric population. Pediatrics. 2020;146(2):e20192629–11. https://doi.org/10.1542/peds.2019-2629
24 Radwan MM, Chandra S, Gul S, ElSohly MA. Cannabinoids, phenolics, terpenes and alkaloids of cannabis. Molecules. 2021;26(9):2774. https://doi.org/10.3390/molecules26092774
25 Mackie K. Cannabinoid receptors: where they are and what they do. J Neuroendocrinol. 2008;20(Suppl 1):10–4. https://doi.org/10.1111/j.1365-2826.2008.01671.x
26 National Conference of State Legislatures. State medical cannabis laws [Internet]. 2024 [cited 2024 Mar 11]. Available from: https://www.ncsl.org/health/state-medical-cannabis-laws
27 Mahabir VK, Merchant JJ, Smith C, Garibaldi A. Medical cannabis use in the United States: a retrospective database study. J Cannabis Res. 2020;2(1):32. https://doi.org/10.1186/s42238-020-00038-w
28 Mahabir VK, Smith CS, Vannabouathong C, Merchant JJ, Garibaldi AL. Comparing medical cannabis use in 5 US states: a retrospective database study. J Cannabis Res. 2021;3(1):15. https://doi.org/10.1186/s42238-021-00075-z
29 Boehnke KF, Dean O, Haffajee R, Hosanagar A. U.S. Trends in registration for medical cannabis and reasons for use from 2016 to 2020: an observational study. Ann Intern Med. 2022;175(7):945–51. https://doi.org/10.7326/M22-0217
30 Boehnke KF, Gangopadhyay S, Clauw DJ, Haffajee RL. Qualifying conditions of medical cannabis license holders in the United States. Health Aff. 2019;38(2):295–302. https://doi.org/10.1377/hlthaff.2018.05266
31 Fairman BJ. Trends in registered medical marijuana participation across 13 US states and District of Columbia. Drug Alcohol Depend. 2016;159:72–9. https://doi.org/10.1016/j.drugalcdep.2015.11.015
32 Nutt D, Bazire S, Phillips LD, Schlag AK. So near yet so far: why won't the UK prescribe medical cannabis? BMJ Open. 2020;10(9):e038687. https://doi.org/10.1136/bmjopen-2020-038687
33 Schlag AK. An evaluation of regulatory regimes of medical cannabis: what lessons can Be learned for the UK? Med Cannabis Cannabinoids. 2020;3(1):76–83. https://doi.org/10.1159/000505028
34 Asselin A, Lamarre OB, Chamberland R, McNeil S-J, Demers E, Zongo A. A description of self-medication with cannabis among adults with legal access to cannabis in Quebec, Canada. J Cannabis Res. 2022;4(1):26. https://doi.org/10.1186/s42238-022-00135-y

35 Wong SS, Wilens TE. Medical cannabinoids in children and adolescents: a systematic review. Pediatrics. 2017;140(5):e20171818. https://doi.org/10.1542/peds.2017-1818
36 Smegal LF, Vedmurthy P, Ryan M, Eagen M, Andrejow NW, Sweeney K, et al. Cannabidiol treatment for neurological, cognitive, and psychiatric symptoms in sturge-weber syndrome. Pediatr Neurol. 2023;139:24–34. https://doi.org/10.1016/j.pediatrneurol.2022.10.014
37 Ananth P, Revette A, Reed-Weston A, Das P, Wolfe J. Parent and patient perceptions of medical marijuana in the childhood cancer context. Pediatr Blood Cancer. 2021;68(4):e28830. https://doi.org/10.1002/pbc.28830
38 Erridge S, Holvey C, Coomber R, Hoare J, Khan S, Platt MW, et al. Clinical outcome data of children treated with cannabis-based medicinal products for treatment resistant epilepsy—analysis from the UK medical cannabis Registry. Neuropediatrics. 2023;54(3):174–81. https://doi.org/10.1055/a-2002-2119
39 Vaillancourt R, Moreno M, Pouliot A, Sell E. Cannabis use for therapeutic purposes by children and youth at a tertiary teaching hospital in Canada: a retrospective chart review. Can J Hosp Pharm. 2020;73(2):105–15. https://doi.org/10.4212/cjhp.v73i2.2976
40 Zürcher K, Dupont C, Weber P, Grunt S, Wilhelm I, Eigenmann DE, et al. Use and caregiver-reported efficacy of medical cannabis in children and adolescents in Switzerland. Eur J Pediatr. 2022;181(1):335–47. https://doi.org/10.1007/s00431-021-04202-z
41 Aran A, Harel M, Cassuto H, Polyansky L, Schnapp A, Wattad N, et al. Cannabinoid treatment for autism: a proof-of-concept randomized trial. Mol Autism. 2021;12(1):6. https://doi.org/10.1186/s13229-021-00420-2
42 Guy W ECDEU assessment manual for psychopharmacology. U.S. Department of health, education, and welfare, public health service, alcohol, drug Abuse, and mental health administration, national Institute of mental health, psychopharmacology research branch. Division of Extramural Research Programs; 1976.
43 Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry. 2007;4(7):28–37.
44 Barkley RA, Edelbrock C. Assessing situational variation in children's problem behaviors: the Home and School Situations Questionnaires. Advances in behavioral assessment of children and families [Internet]. Greenwich, CT: JAI Press Inc.; 1987 [cited 2024 Jan 10]. p. 157–76. Available from: https://scholar.google.com/scholar_lookup?title=Advances+in+behavioral+assessment+of+children+and+families&author=RA+Barkley&author=C+Edelbrock&publication_year=1987&
45 Edelson S, Rimland B Autism treatment evaluation checklist (ATEC). San Diego, CA: Autism Research Institute; 1999.
46 Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: childhood Autism Rating Scale (CARS). J Autism Dev Disord. 1980;10(1):91–103. https://doi.org/10.1007/BF02408436
47 Nutt DJ, King LA, Nichols DE. Effects of Schedule I drug laws on neuroscience research and treatment innovation. Nat Rev Neurosci. 2013;14(8):577–85. https://doi.org/10.1038/nrn3530
48 Hutchison KE, Bidwell LC, Ellingson JM, Bryan AD. Cannabis and health research: rapid progress requires innovative research designs. Value Health. 2019;22(11):1289–94. https://doi.org/10.1016/j.jval.2019.05.005
49 Kelly LE, Rieder MJ, Finkelstein Y. Medical cannabis for children: evidence and recommendations. Paediatr Child Health. 2024;29(2):104–21. https://doi.org/10.1093/pch/pxad078
50 Graham M, Martin JH, Lucas CJ, Murnion B, Schneider J. Cannabidiol drug interaction considerations for prescribers and pharmacists. Expert Rev Clin Pharmacol. 2022;15(12):1383–97. https://doi.org/10.1080/17512433.2022.2142114
51 Doucette ML, Hemraj D, Bruce D, Fisher E, Macfarlan DL. Medical cannabis patients under the age of 21 in the United States: description of demographics and conditions from a large patient database, 2019-2023. AHMT. 2024;15:63–72. https://doi.org/10.2147/AHMT.S460560
52 Sakal C, Lynskey M, Schlag AK, Nutt DJ. Developing a real-world evidence base for prescribed cannabis in the United Kingdom: preliminary findings from Project Twenty21. Psychopharmacology. 2022;239(5):1147–55. https://doi.org/10.1007/s00213-021-05855-2
53 Wang SV, Schneeweiss S. Assessing and interpreting real-world evidence studies: introductory points for new reviewers. Clin Pharmacol Ther. 2022;111(1):145–9. https://doi.org/10.1002/cpt.2398
54 Schlag AK, Zafar RR, Lynskey MT, Athanasiou-Fragkouli A, Phillips LD, Nutt DJ. The value of real world evidence: the case of medical cannabis. Front Psychiatry. 2022;13:1027159. https://doi.org/10.3389/fpsyt.2022.1027159