Safety of cannabinoids used for medical purposes in children and adolescents

by

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Thesis Abstract

Background: Over the last two decades, there has been growing interest and research in using cannabinoids for medical purposes in children. The main goal of my doctoral thesis was to examine the safety of cannabinoids used for medical purposes in children to generate data to guide clinical practice and future research.

Methods: First, we conducted a living systematic review (LSR) to study the available evidence on cannabis products used for medical purposes in children. Second, to learn more about specific indications and safety profiles, we conducted three separate subgroup systematic reviews of studies including children with cancer, autism spectrum disorder (ASD), and a subgroup analysis of randomized controlled trials where adverse event (AEs) profiles were compared between those receiving cannabinoids and control arms. Third, a pharmacovigilance database study was conducted to evaluate the real-world safety reporting on cannabidiol (CBD) and investigate its drug interactions in children.

Results: In the LSR, among identified interventional and observational studies, common indications for cannabinoids in children were refractory epilepsy (n=146 studies, 188,726 participants), followed by cancer and cancer symptom management (n=30 studies, 208,753 participants), and ASD (n=18 studies, 1285 participants). The most common cannabinoids studied in interventional studies were purified CBD (78.6%, n=66 studies, 5235 participants) with dose-range of 2-50 mg/kg/day, tetrahydrocannabinol (THC) (6%, n=5 studies, 148 participants) with dose-range of 2.5-10 mg/day (with a max dose of nabiximols containing 32.4 mg of THC) and nabilone (6%, n=5 studies, 267 participants) with dose-range of 0.5-2 mg/day. In a cancer symptom management systematic review, cannabinoids were commonly used for

chemotherapy-induced nausea and vomiting (11/19, 58%) management. In controlled studies, somnolence, dizziness, dry mouth, and withdrawal due to adverse events were more commonly associated with the use of cannabinoids in children with cancer compared to active control group. In the ASD review, the pooled prevalence of AEs across single-arm studies and observational studies was 44.8% (95% CI, 24.1-67.4; I2 = 94%; 9 studies) in children with ASD. Somnolence, changes in appetite, restlessness, and tiredness were the commonly reported AEs (> 10%). Validated efficacy measures were reported inconsistently across studies. Epilepsy, sleep impairment, hyperactivity, concentration impairment, and irritability were the most common symptoms managed with cannabinoids in children with ASD. In a meta-analysis of randomized controlled clinical trials, cannabinoids were associated with an overall increased risk of adverse events (risk ratio [RR], 1.09; 95% CI, 1.02-1.16; I^2 = 54%; 12 trials), withdrawals due to adverse events (RR, 3.07; 95% CI, 1.73-5.43; I^2 = 0%;14 trials), and serious adverse events (RR, 1.81; 95% CI, 1.21-2.71; I^2 = 59%; 11 trials) compared with control group. In real-world pharmacovigilance data, Signals were detected for hospitalization [Proportional Reporting Ratio (PRR) 30.83 (95% CI, 26.03-36.51), 127 reports], sudden unexplained death in epilepsy [PRR 27.64 (95% CI, 10.06-75.91), 4 reports], seizures [PRR 19.77 (95% CI, 18.03-21.66), 328 reports] and death [PRR 14.07 (95% CI, 12.27-16.13), 176 reports]. CBD was commonly reported to interact with clobazam (n=8/19, 42.10%), valproic acid (n=4/19, 21.05%), mTOR inhibitors (everolimus and sirolimus; n=3/19, 15.78%), topiramate (n=2/19, 10.50%), and zonisamide (n=2/19, 10.50%).

Conclusions This thesis's findings identified evidence gaps while synthesizing dosing, safety, and reported benefits of cannabinoid use in children for medical purposes. Long-term

safety studies, especially those exploring cannabinoid-related drug interactions and tools that improve adverse event reporting and harmonize cannabis exposure definitions, are needed.

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Dedication

I dedicate this thesis to

- To my father, Narinder Kumar, who watches over me from heaven.
- To my maternal grandfather, Ranvir Trehan, whose strength and wisdom continue to inspire me.

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Preface

This thesis is written in a grouped manuscript style, where each chapter/section represents a published manuscript or is considered for publication in peer-reviewed journals (see below). The manuscripts included in this thesis were conceptualized, executed, written, and revised by Manik Chhabra in collaboration with his thesis supervisor, Dr. Lauren E Kelly, and advisory committee Drs. Geert W.'t Jong, Sachin Katyal, and Sapna Oberoi, along with additional experts from the C4T academic research group, including Drs. Holly Mansell and Yaron Finkelstein, and an experienced health sciences librarian, Mê-Linh Lê at the University of Manitoba. Manik Chhabra takes complete guarantee and responsibility for the integrity, accuracy of analysis, and interpretation of the manuscripts. All manuscripts have been revised based on feedback received from co-authors, and final approval was obtained from them before publication.

This thesis includes five chapters: Chapter 1 covers the introduction and rationale; Chapter 2 summarizes evidence on cannabinoid use in children from available studies, including four manuscripts (sections 2.1, 2.2, 2.3, and 2.4). Chapter 3 describes real-world evidence on CBD-related adverse events and drug interactions (fifth manuscript). Finally, Chapter 4 provides conclusions and directions for future research, and Chapter 5 contains supplementary material.

Manuscripts are accepted, submitted, or prepared for publication in peer-reviewed journals. The five manuscripts included in this thesis are as follows:

- **Section 2.1:** Chhabra M, Paul A, Abulannaz A, Lê ML, Mansell H, Finkelstein Y, Huntsman RJ, Kelly LE. Cannabinoids for Medical Purposes in Children: A Living Systematic Review. Acta Paediatrica (under peer review).
- **Section 2.2:** Chhabra M, Ben-Eltriki M, Paul A, Lê ML, Herbert A, Oberoi S, Bradford N, Bowers A, Rassekh SR, Kelly LE. Cannabinoids for symptom management in children with cancer: A systematic review and meta-analysis. Cancer. 2023;129(22):3656-3670.
- **Section 2.3:** Chhabra M, Pawliuk C, Lim E, Lê ML, Mansell H, Siden H, Rassekh RS, Oberlander, TF, Kelly LE. Cannabinoids used for symptom management in children with autism spectrum disorder: A systematic review and meta-analysis.
- **Section 2.4:** Chhabra M, Ben-Eltriki M, Mansell H, Lê ML, Huntsman RJ, Finkelstein Y, Kelly LE. Cannabinoids used for medical purposes in children and adolescents: A systematic review and meta-analysis. JAMA Pediatrics. 2024; 9(25).
- **Chapter 3:** Chhabra M, Plebon-Huff S, Jong W. 't, Lê ML, Finkelstein Y, Graham M, Kelly LE. Real-world safety of cannabidiol and its clinical drug interactions in children and adolescents: insights from pharmacovigilance study and systematic literature review.

Chapter 1 Introduction and rationale

1.1 History and global landscape of cannabis used for medical purposes

The cannabis plant has been cultivated for recreational, industrial, and medical purposes since ancient civilizations.(1) Cannabis species belong to the family *Cannabaceae*, and the common species in this genus are *Cannabis indica*, *ruderalis,* and *sativa*.(2) The first documented medical use of cannabis dates to the third millennium BC in King Shen Nung's (a Chinese emperor) pharmacopeia.(3) Medical use of cannabis is also documented in the historical scripts of Assyrians, Greeks, Indians, and Romans.(3) In the Indian system of medicine (Ayurveda), cannabis has been used for eons to manage pain, nausea, loss of appetite, insomnia, anxiety, and spasticity.(4) Firsthand evidence informs that around 400 A.D., cannabis was used for medical purposes in North America.(5) In 1841, William O'Shaughnessy, an Irish medical doctor, unveiled cannabis to the West following his long practice in East India; he wrote about the versatility of cannabis in stopping convulsions in children.(6) In the late 19th and early 20th century, cannabis was well-known as a patent medicine in the US.(1) Later, in 1850 cannabis was registered as a medication in the US Pharmacopoeia.(7) In 1937, the Marihuana Tax Act was passed, restricting the sales and use of cannabis in the US.(7) Three years after the Marihuana Tax Act, cannabis was dropped from the US Pharmacopeia(8) Through the Controlled Substance Act of 1970, the US federal government imposed restrictions on cannabis and classified it as a drug with no medical use.(7, 9) This restricted both medical use and research on cannabis in the US.

In 1999, Canada(10) and Israel(11) were the first nations to allow cannabis use for medical purposes, followed by the Netherlands in 2003,(12) Switzerland in 2011,(13) Czechia in

2013,(14) Australia in 2016,(15) and Germany in 2017.(16) The legal framework regulating access to cannabis use for medical purposes in Canada evolved with time: first Marihuana Medical Access Regulations (2001), followed by Marihuana for Medical Purposes Regulations (2013), Access to Cannabis for Medical Purposes Regulations (2016), and the most recent Cannabis Act (Bill C-45) (2018).(17) Under the framework of Health Canada, the Cannabis Act created two separate streams for accessing cannabis for medical and recreational reasons.(18) Over the last decade, global medical cannabis laws have changed completely and captured much attention.(18) However, the stigma surrounding ethical, legal, and societal considerations limits its use for medical purposes.(19, 20)

1.2 Epidemiology of medical cannabis use

Cannabis has gained popularity for medical use among both adults and children with ease in global cannabis laws and regulations.(21) In Canada, Health Canada regulates medical cannabis access under the framework of the Cannabis Act (S.C. 2018, c. 16),(22) which allows access to medical cannabis with authorization from a healthcare practitioner.(22) As of December 2023, 183,909 individuals in Canada were registered to access cannabis for medical reasons under the Cannabis Act, 2018.(22) Post-legalization of recreational cannabis in Canada (October 2018), there has been a 46.7% decline in medical cannabis registrations.(23) In Canada, many people access cannabis for medical reasons from the recreational market without authorization from healthcare practitioners.(24) Age-stratified data on cannabis use for medical reasons among Canadian children (≤18 years old) are not available. A survey conducted among 10,269 Ontario adults reported that 66% of respondents accessed cannabis for chronic conditions or musculoskeletal pain.(25) Another survey, including 175 (22%) participants who were children or caregivers of children from the US reported cannabis use for different medical

conditions, including neurological conditions (n=307/808, 38%), chronic pain (n=204/808, 25%), followed by neuropsychiatric conditions (n=146/808, 18%), autoimmune conditions (n=75/808, 9%), cancer (n=59/808, 7%), and insomnia (n=6/808, 1%).(26) There is an increase in self-reported cannabis product use for medical reasons through the recreational market.(27) An epidemiological survey reported a 27% prevalence (n=7,336) of self-reported medical cannabis use in North America. Further, survey reported higher prevalence of self-reported cannabis use in US legal-recreational states (2,515/7,398, 34%) vs US legal medical use states (1,528/6,018, 25.4%) vs US-illegal recreational states (843/3,696, 22.8%), and Canada (2,484 /10,057, 24.7%).(27)

In a multinational survey on medical cannabis use, 94.8% (n=903/953) of participants reported using cannabis-based medicines via inhalation (smoking) route, while 68.5% (n=653/953) reported oral or sublingual route of administration.(28) Further, commonly reported indications for medical cannabis were chronic pain (n=278/953), anxiety (n=175/953), loss of appetite (n=102/953), depression (n=50/953), and insomnia (n=49/953).(28) A survey conducted among Manitoban patients and caregivers of children with cancer at a pediatric cancer care facility reported that 22% (n=14/64) of participants used medical cannabis for either symptom management or cancer treatment.(29) A study conducted in Italy reported that 40% (n= 27/66) of adolescents and young adults used cannabis for cancer symptom management, including anxiety, nausea, pain, sleep, and anorexia.(30) Another study involving 56 Canadian neurologists treating 668 children with epilepsy reported that 68% and 64% of neurologists considered cannabinoids as a therapeutic option for children (non-responders to an average four antiepileptic drugs) with Dravet Syndrome and Lennox-Gastaut Syndrome.(31) An epidemiological survey conducted

among caregivers of children (aged 5 to 10 years) with autism reported that 84.5% (347/568) of caregivers were willing to use cannabis in their children with autism.(32)

Mapping data on medical cannabis use in children is challenging, both nationally and internationally as medical cannabis laws and products are quite variable across jurisdictions.(19, 33) Additionally, medical cannabis products may vary in formulations (oils, gummies, edibles, etc.), contents (CBD:THC ratios), and doses.(34) Further, medical cannabis products are not assigned unique drug identification numbers, making it challenging to record and track their usage using administrative databases.(35) Moreover, due to societal barriers and stigma surrounding medical cannabis, parents are reluctant to report its use in their children.(36) Most of the data on medical cannabis use come from self-reporting, which can introduce reporting and information biases.(37) Literature on medical cannabis use in children also lacks data on dosage, formulations, and CBD:THC ratios.(34) Due to the lack of standardized reporting, it is challenging to summarize data on medical cannabis use in children and compare its safety and efficacy outcomes across studies in children. Medical cannabis regulatory framework varies across jurisdictions, impacting both research and clinical practice of medical cannabis in children. Researcher face challenges in securing standard medical cannabis formulations, and limited incentives to conduct clinical trials.

1.3 Endocannabinoid system

Cannabinoids act through the endocannabinoid system (ECS).(38) The role and functioning of the ECS are essential to understand the mechanism of unintended effects associated with cannabinoid use for medical purposes in children.(38) Given the widespread

distribution of the ECS throughout the body, cannabinoids may act off-target leading to undesired effects.(38) Unintended effects of cannabinoids used for medical purposes are mediated through the ECS in children with developing physiological needs.(39, 40) Cannabinoids used for medical purposes also have the potential to interact with other medications, especially CBD.(40-43) Cannabinoids may cause unintended effects through the ECS and drug interactions in children receiving multiple medications.(40-43)

1.3.1 Components of Endocannabinoid system

Cannabinoids act through the ECS, which comprises of specific neurotransmitters called endocannabinoids (eCBs), cannabinoid receptors (CB1 and CB2), and enzymes responsible for the synthesis and degradation of eCBs.(32) The ECS plays a vital role in regulating sleep, appetite, cognition, and neuronal conduction.(32, 44) Two eCBs derived from the phospholipid layer in the body are N-arachidonoyl-ethanolamide/anandamide (AEA) and 2-arachidonoyl glycerol (2-AG).(32, 45) Enzymes such as N-acyl phosphatidylethanolamine hydrolase phospholipase D, diacylglycerol lipase-α (DAGL-α), and -β (DAGL-β) synthesize eCBs, while fatty acid amide hydrolase (FAAH) and monacylglyceride lipase (MAGL) degrade eCBs.(46)

1.3.2 ECS functioning and role in homeostasis

Cannabinoids act through CB1 and CB2 receptors located on presynaptic junctions, regulating the release of excitatory and inhibitory neurotransmitters.(38, 47, 48) CB receptors are G-protein coupled receptors (GPCRs).(49, 50) They regulate electrical activity in the brain, pain, cognition, and other biological processes in living organisms.(38, 47, 51)

CB1 receptors are ubiquitously expressed in the cerebral cortex, central gray matter, hypothalamus, and cerebellum.(52) They are also expressed on the presynaptic membranes in

both central and peripheral nervous systems. CB1 receptors regulate cognition, mood, concentration, thought processes, learning, and motor coordination.(53) Endocannabinoids and exogenously administered cannabinoids like THC act as ligands on CB1 receptors and activate the Gi signaling protein. Further, this decreases cellular cyclic adenosine monophosphate (cAMP) levels by inhibiting adenyl cyclase (AC), an enzyme responsible for production of cAMP, leading to inhibition of calcium channels and opening of G-protein-coupled inwardly rectifying potassium channels (GIRK).(52-54)

CB2 receptors are expressed on the immune cells and play a immune modulatory role.(55) They regulate release of cytokines in blood.(56) Recent studies have reported expressions of CB2 receptors on microglia, astrocytes, and neurons.(57) Unlike CB1 receptor, CB2 receptors do not produce psychotropic effects.(47) When cannabinoids bind to CB2 receptors, they activate the Gi/o pathway, stimulating the mitogen-activated protein kinase (MAPK) and the PI3K/AKT/mTOR pathway, also known as the PAM signaling pathway. This network of intracellular signals regulate cell growth, survival, and cycle cycles. Cannabinoids also modulate apoptosis, proliferation, and cell growth.(47) **Figure 1.1. and 1.2.** illustrate CB1 and 2 receptors signal transduction pathways. Cannabinoid receptors also have physiological roles in the cardiovascular system,(58) urological system,(59) skeletal muscles,(60) reproductive,(61) and gastrointestinal systems.(43) Activation of both CB1 and 2 receptors increase blood pressure, heart rate, and cause dryness in the throat and mouth (anticholinergic effects). Psychoactive effects associated with their CB1 receptors activation include decreased motor coordination, euphoria, irritability, and increased perception and joy.(38, 58)

1.3.3 ECS disruption in neurological disorders

Fibromyalgia, irritable bowel syndrome, migraine, and other complex health challenges have been linked to lower levels of plasma eCBs, also known as eCB deficiency syndromes.(62) Neuronal conductivity and plasticity are regulated through endocannabinoid signaling.(40) Dysregulation of ECS conductivity has been reported in children with refractory epilepsy and autism spectrum disorder.(39, 63) A comparative gene expression profiling was performed in patients with intractable temporal lobe epilepsy (TLE) compared to healthy controls.(64) CB1 receptors were downregulated in patients with intractable TLE compared with healthy control, along with a 60% reduction in DAGL-α mRNA expression, the enzyme synthesizing 2-AG.(64)

Studies report lower levels of eCBs(63) and upregulation of CB1 and CB2 receptors in children with autism.(65) Similar findings of reduced eCBs were reported in valproic acid (VPA)-induced autism spectrum disorder (ASD) preclinical models (following prenatal VPA exposure).(65) In a VPA-induced ASD rat model, treatment with JZL184, a selective MAGL inhibitor, increased plasma 2-AG levels. Further, elevated plasma 2-AG levels were associated with improvement in spectrum of autism-related symptoms including, hyperactivity, sociability, social preference, cognitive functioning, stereotypical and repetitive behaviors.(65)

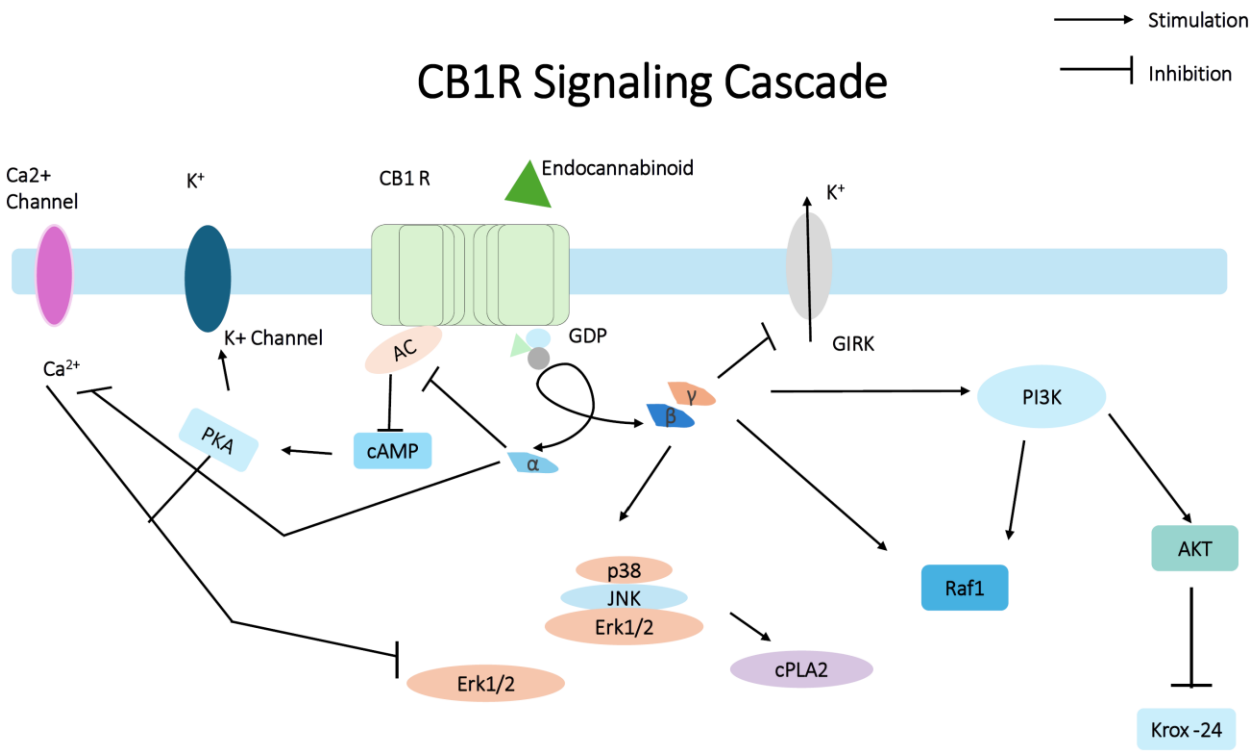


Figure 1.1. CB1 receptor signaling transduction pathway.

Abbreviations AC Adenyl Cyclase, cAMP Cyclic adenosine monophosphate, Erk1/2, Extracellular receptor kinase 1 and 2, GDP Guanosine diphosphate, GIRK G protein-coupled Inwardly Rectifying Potassium channels, PKA Protein kinase A, JNK Jun N-terminal Kinase, PL3K Phosphoinositide 3-Kinase.

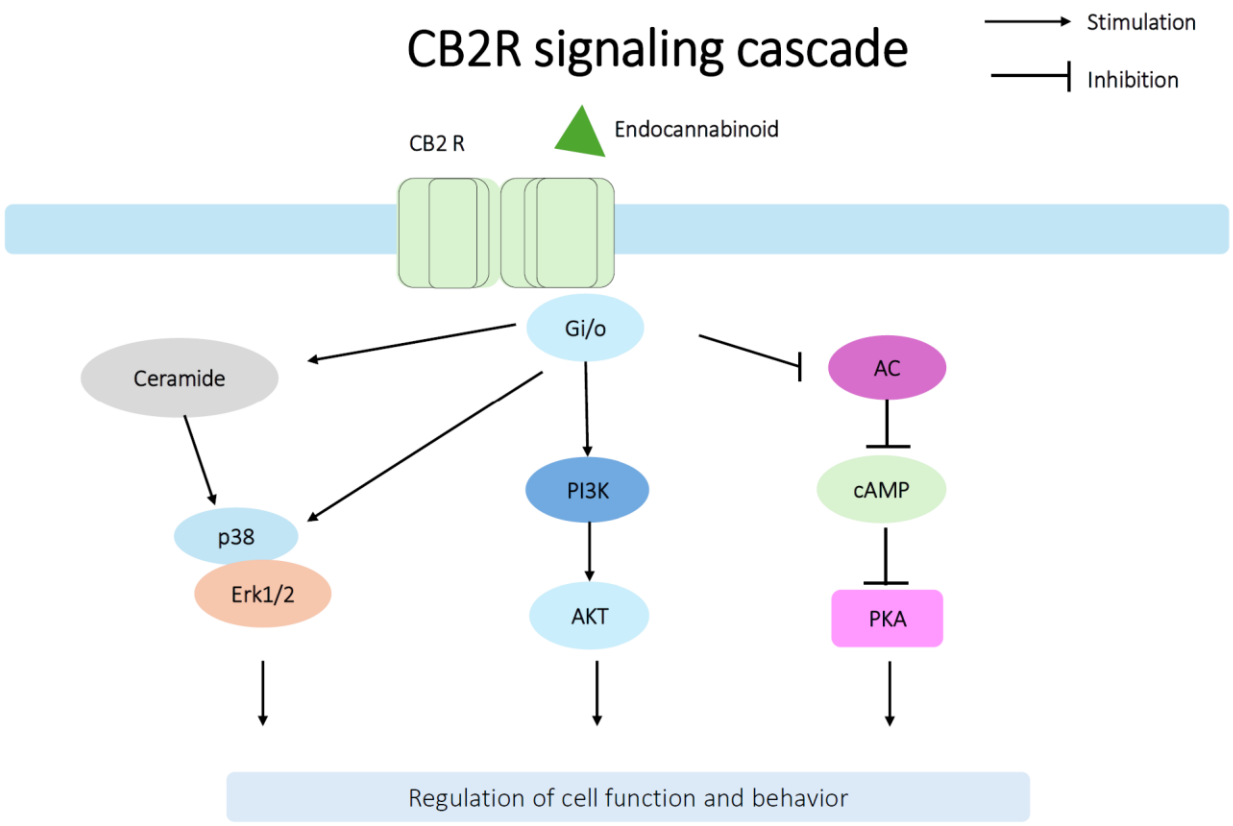


Figure 1.2. CB2 receptor signaling transduction pathway.

Abbreviations AC Adenyl Cyclase, Erk1/2, Extracellular receptor kinase 1 and 2, PKA Protein kinase A, PI3K Phosphoinositide 3-Kinase.

1.3.4 Efficacy of cannabinoids in animal models

Cannabinoids have demonstrated analgesic effect in acute and chronic pain experimental animal models through both cannabinoid receptors and by elevating endocannabinoid levels at presynaptic membranes.(66) Furthermore, they exert nociceptive actions by inhibiting both ascending and descending pain pathways.(67) Cannabinoids have also shown promising results in managing neuropathic pain by inhibiting both hyperalgesia and allodynia in animal models.(68) Chronic CBD administration was helpful in managing pain in an inflammatory pain rat model.(69) In mice model of neuropathy, medium to high dose of CBD was reported to inhibit thermal hypersensitivity and tactile allodynia.(70) CBD was more promising in attenuating pain when administered at early stages of disease.(67, 69)

Animal studies report the antiemetic potential of delta-9 THC, and synthetic derivatives of THC (nabilone and dronabinol) because of their binding to CB1 receptors.(71) CB1 receptors are expressed in the emetic control zone in the midbrain.(72) Delta-8 THC was reported superior in controlling nausea than delta-9 THC in in-vivo studies.(73) Animal studies also suggest that delta-9 THC's antagonism over 5-HT3 receptors is responsible for its antiemetic effects.(74) CBD act as an agonist over somatodendritic 5-HT1A auto receptors expressed on the dorsal raphe nucleus and supresses nausea and vomiting. In animal model when 2.5 mg/kg CBD was combined with 1 mg/kg THC, this led to significant control in acute nausea and vomiting.(75) However, it is challenging to study chemotherapy-induced nausea and vomiting management in rodent models due to their lack of emetic reflexes.(76) Researcher often use indirect behaviours such as consumption of non-nutritive substances such as clay, these method often fail to reciprocate complete human conditions for nausea and vomiting.(77) Moreover, most of the

animal studies use healthy animals rather than tumor models to study the side effects of chemotherapeutic drugs such as nausea and vomiting.(76)

1.4 Cannabinoids

Cannabinoids, terpenes, and flavonoids are the active constituents of the cannabis plant.(2) The broader classification of cannabinoids includes phytocannabinoids (derived from the cannabis sativa plant), endocannabinoids (eCBs) (endogenous lipid-based neurotransmitters), and pharmaceutically produced cannabinoids (synthesized in the laboratory).(78) Phytocannabinoids are obtained from the dried buds of the cannabis plant; these buds are used to prepare cannabis formulations (cannabis herbal extracts/oils).(79) Cannabidiol (CBD), cannabinol (CBN), cannabichromene (CBC), cannabigerol (CBG), and tetrahydrocannabinol (THC) are phytocannabinoids, with CBD and THC being the most predominant.(80)

CBD and THC are the foremost explored phytocannabinoids because of their therapeutic potential.(2, 79) Endocannabinoids (eCBs) are synthesized within the body; AA and 2-AG are two known eCBs.(81) Pharmaceutical cannabinoids with marketing authorization include nabilone and dronabinol.(82) Currently, none of these have a pediatric indication except for purified CBD.(83) Regulatory authorities have approved the use of purified CBD in children (aged 1 or greater, depending on jurisdiction) with drug-resistant epilepsies, including Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex.(84) Cannabinoids are available in various forms, including dried herbs (flowers), plant-based extracts, resins, oils, and synthetic preparations.(84)

Terpenes and flavonoids present in the cannabis plant also exhibit pharmacological properties.(85, 86) Around 200 unique terpenes are found in the cannabis plant as resins and essential oils. Terpenes are hydrocarbons with lipophilic properties and distinct aroma characteristics.(87) They act both independently and synergistically with other cannabinoids, leading to analgesic, antidepressant, and neuroprotective effects.(86) Terpenes are believed to enhance the therapeutic action of cannabinoids by facilitating THC binding to CB1 receptors.(88) Common terpenes present in the cannabis plant include linalool, limonene, terpinolene, ocimene, myrcene, and valencene.(86)

Flavonoids are another group of phytocannabinoids with a phenolic ring present naturally in the cannabis plant. (86, 88) Cannflavins are the common flavonoids present, with three different types: cannflavin A, cannflavin B, and cannflavin C.(86, 89) Flavonoids possess strong anti-neuroinflammatory properties and are 30 times more potent than aspirin in inhibiting prostaglandin release in in-vitro experiments.(89) Given the complex nature of cannabis, the therapeutic potential of terpenes, flavonoids, and other minor cannabinoids has not yet been explored.

1.4.1 Cannabidiol

Cannabidiol (CBD) is a phytocannabinoid with multiple pharmacological actions; it acts on more than 65 molecular targets, including transporters, receptors, ion channels, and enzymes.(90) CBD acts as an inverse agonist or antagonist on both the CB receptors.(91) CBD also acts a negative allosteric modulator on CB1 receptor.(91, 92) CBD increases blood levels of eCBs (AA and 2-AG) by inhibiting enzymes responsible for their degradation—monoacylglycerol lipase and fatty acid amide hydrolase.(93) It also inhibits reuptake of AA and 2-AG, increasing their concentration and duration of action.(93) CBD has a low binding affinity

towards CB1 receptors, making it less intoxicating compared to THC.(94) Intoxication with products containing both CBD and THC can lead to psychological (euphoria, impaired cognition, anxiety, and paranoia) and physical (increased appetite, tachycardia, motor impairment, and dry mouth) manifestations.(95, 96) Repetitive CBD administration with THC result in antinociceptive effects.(97, 98) CBD inhibits the metabolism of THC and leads to negative allosteric modulation of CB1 receptors (THC antagonism); this mechanism results in tolerance development and increases demand for higher daily doses of cannabis-based products.(97, 98) At higher dose levels, CBD increases the risk of lethargy and somnolence.(97) It may also cause unfavorable effects due to drug interactions and formulation-related issues (such as impurities, contamination of THC, and poor quality).(99, 100)

CBD is a lipophilic molecule with more than 94% protein binding, a high volume of distribution ranging between 20963- 42849 L, and significant enterohepatic circulation, which prolongs its half-life.(94) CBD can be administered through different routes, including inhalation, oral, sublingual, and tropical.(101) Common CBD-related formulations include oils, solutions, sprays, gummies, and transdermal gels.(101) Plasma half-life of CBD is long, depending on the route of administration, ranging from 24 hours (venous route) to 31 hours (inhalation route).(102) CBD has been used as an intervention in randomized controlled trials (RCTs) exploring its safety and efficacy in children with drug-resistant epilepsies, fragile X syndrome, treatment of cannabis use disorder, and autism spectrum disorder.(84) In RCTs, CBD-related adverse events were dose-related, especially when the CBD doses were titrated more than 20mg/kg/day. The most common CBD-related adverse events reported in the RCTs were nausea, diarrhea, somnolence, changes in appetite, and headache.(103) CBD-induced diarrhea and nausea are linked to its interaction with 5-hydroxy-tryptamine and cannabinoid receptors present

in the gut.(104) CBD acts on the ECS and regulates appetite, and weight.(105) Furthermore, CBD also increases GABA levels in the central nervous system. Its interaction with 5HT1A receptors and increased GABA levels result in somnolence and sedation.(106)

1.4.2 Tetrahydrocannabinol

Tetrahydrocannabinol (THC), also known as delta-9 THC, is the primary psychoactive component derived from the cannabis plant.(107) THC strongly binds to CB1 receptors and regulates appetite, nausea, vomiting, and pain.(92) When THC binds to CB1 receptors, it leads to analgesic, cataplexic, and hypothermic responses. THC has a weak binding affinity towards CB2 receptors; however, through CB2 receptors, it induces anti-spasmodic, anti-inflammatory, and neuroprotective responses.(92) THC products are available with CBD in different formulations, including tablets, capsules, and cannabis herbal extracts in varying ratios (CBD:THC, 1:1 balanced; THC dominant, 60-98%; and THC products, >98%).(101) Dronabinol is pharmaceutical derivative of THC approved by the US Food and Drug Administration for chemotherapy-induced nausea and vomiting (CINV) management in adults.(108, 109) However, its use is off-label in children. Dronabinol increases appetite; it is used for Acquired Immuno-Deficiency Syndrome (AIDS)-related anorexia management.(108) In the late 1980s, RCTs demonstrated the efficacy of THC for CINV management in children and adolescents.(110-113) Euphoria, tachycardia, confusion, hypotension, and paranoia were common THC-related adverse events reported in RCTs.(110, 111)

THC-related euphoria after its intoxication is result of activation of CB1 receptors,(38) increase in dopamine release and neuronal activity,(114) and increase in frontostriatal connectivity between the nucleus accumbens and medial prefrontal cortex (results in feelings of

pleasure and reward).(115) THC activates CB 1 and 2 receptors, resulting in increase in blood pressure and heart rate.(116)

1.4.3 Cannabis herbal extracts

Cannabis-herbal extracts (CHE) are available in different THC and CBD ratios, including 1:20, 1:25, and 1:1. (101) Classification of CHEs based on THC and CBD ratios according to Australian Therapeutic Goods and Administration classification includes CBD-cannabis products (CBD ≥98%), CBD-dominant cannabis products (CBD ≥60% and <98%), balanced-cannabis products (<60% and ≥ 40%), THC-dominant medicinal cannabis products (THC 60% to 98%), and THC cannabis products (THC >98%).(117) Nabiximols (also known as Sativex) is a cannabis herbal extract spray with a balanced THC: CBD ratio; it is used in children with spasticity related to traumatic brain injury and cerebral palsy.(118) When high CBD and low THC ratios are used together, CBD mitigates THC's psychoactive effects.(119) Whole plant-based cannabis herbal extracts are used for management of autism spectrum disorder-related symptoms in children(120) Observational studies report that whole plant-based cannabis herbal extracts are efficacious in reducing seizures and improving the quality of life in children with drug-resistant epilepsies.(121)

1.4.4 Nabilone

Nabilone is a pharmaceutical derivative of THC available in capsules.(82) The US FDA and Health Canada have approved nabilone for refractory CINV management in adults.(109, 122) However, its use in children is off-label. Nabilone directly acts on CB1 receptors, inhibiting neuronal reflexes of nausea and vomiting.(109) RCTs from the 1980s report superior efficacy of nabilone for CINV management compared to active control in children. A recent treatment chart review from Canada reports the use of nabilone for symptom management in children with

cancer.(123) Nabilone gets rapidly and completely absorbed, with a plasma half-life of 2 hours. Its volume of distribution is 12.5 l/kg, and the main route of excretion is bile.(124) Xerostomia, blurred vision, orthostatic hypotension, ataxia, drowsiness, and depression were commonly reported nabilone-related adverse events in RCTs.(124)

1.4.5 Dexanabinol

Dexanabinol is a non-psychotropic terpene-based synthetic cannabinoid developed from delta-8 THC without any CB1 and CB2 activity (125) It acts as an non-competitive antagonist over N-methyl-D-aspartate (NMDA) receptors. Dexanabinol depicts neuroprotective activity by attenuating glutamate and NMDA toxicity.(125) Dexanabinol also possesses antioxidant and free radical scavenging properties.(126) Two RCTs investigated the efficacy and safety of dexanabinol in children with traumatic brain injury; it was given as a single intravenous injection at a dose of 150 mg.(127, 128) Due to the lack of clinical efficacy, dexanabinol failed to get marketing authorization. Nuclear factor kappa B (NF-kB) is overactivated in cancerous cells and plays an essential role in cell proliferation.(129) Dexanabinol inhibits NF-kB activity by decreasing the expression of NF-kB genes coding for tumor necrosis factor-alpha, inducible nitric oxide synthase, and cytokines.(130, 131)

1.4.6 Minor cannabinoids

Cannabinoids produced in small amounts in the cannabis plant are known as minor cannabinoids.(80) Very little is known about the complete pharmacological profile of minor cannabinoids. Limited evidence from observational studies suggests that adding minor cannabinoids helps to improve refractory epilepsy and ASD-related symptoms in children.(132)

Acidic (acidic in nature), varinic (derivate of varin family), and neutral (neutral in nature) are broader classifications of minor phytocannabinoids.(80) Cannabidiolic Acid (CBDA), Cannabigerolic Acid (CBGA), and Tetrahydrocannabinolic Acid (THCA) are the acidic minor cannabinoids.(133) CBDA has a lower affinity towards cannabinoid receptors; it acts as an allosteric modulator on 5-HT1a receptors.(80) It possesses analgesic, anti-inflammatory, and antinociceptive properties.(80, 134, 135) CBGA is a precursor for THCA, CBDA, and CBCA;(80) delta-9THC is synthesized from the decarboxylation of THCA. Cannabidivarin (CBDV) and Tetrahydrocannabivarin (THCV) are varinic cannabinoids that bind to both cannabinoid receptors.(80, 136) Neutral minor cannabinoids include Cannabinol (CBN), Cannabichromene (CBC), and Cannabigerol (CBG).(80) Unlike other cannabinoids, CBN is not synthesized in the cannabis plant; it is formed as a result of delta-9 THC degradation.(137) CBN has analgesic and anti-inflammatory properties and a low binding affinity to both cannabinoid receptors.(137) It also acts as an agonist on TRP (transient receptor potential) V1, V2, V3 and V4 channels.(137) CBC decreases cAMP levels through CB1 and CB2 receptors and TRPV1 channels.(138) CBC depicts anticancer, analgesic, anti-inflammatory, and antinociceptive properties.(138) CBD is formed as a result of the decarboxylation of Cannabigerolic Acid (CBGA) in the cannabis plant.(139) CBGA has anti-inflammatory and analgesic properties with low partial agonist activity over both cannabinoid receptors.(139)

1.5 Medical cannabis regulations in Canada

Access to medical cannabis in Canada is regulated under the Cannabis Act of 2018 (Bill c 45, S.C. 2018, c. 16) by Cannabis for Medical Purposes Regulations.(17, 140) Anyone, including children, can access cannabis for medical reasons in Canada with a medical document from their physician or nurse practitioner.(140) Under regulations of the Cannabis Act, patients authorized

for medical cannabis can either purchase it from an authorized retailer/ licensed seller, produce their supply themselves, or designate a third party to produce it for them.(140) People authorized for medical cannabis can possess 150 grams or a 30-day supply of dried cannabis as an add-on supply to 30 grams allowed for non-medical purposes.(140) **Table 1.1.** compares recreational cannabis, medical cannabis, and pharmaceutical cannabinoids.(34)

Table 1.1. Comparison of recreational, medical, and pharmaceutical cannabinoid use.

Recreational cannabis	**Medical cannabis**	**Pharmaceutical cannabinoids**
Adults 18 years or older can access recreational cannabis in Canada.	Physicians must authorize use of cannabis for medical purposes.	Physicians prescribe it for Health Canada-approved indications and sometimes off-label.
No Drug Identification Number (DIN).	No DIN.	Linked with DIN.
No fixed daily dosage.	Strictly as per the authorized daily dosage.	Strictly as prescribed daily dosage.
Purchased online and from stores.	Purchased from a federally licensed seller, register with Health Canada to produce their own (limited	Purchased from the pharmacy after receiving prescriptions from the physician.

	amount) or assign someone to produce.	
Regulated under Good Production Practices.	Regulated under Good production practice.	Regulated under Good Manufacturing Practices.
A variety of cannabis products with different CBD: THC ratios in the form of oils, gummies, vapes, beverages, etc.	CBD, THC, and terpene products in the form of oils, gels, solutions, etc.	Nabilone (capsules), nabiximols (spray), and purified CBD (solution) are available in Canada.

1.6 Cannabinoids used for medical purposes in children

Cannabinoids are used in children for cancer symptom management (nausea, vomiting, anorexia, and pain), drug-resistant epilepsies, autism spectrum disorder, and non-cancerous pain.(84, 141, 142) The claims regarding the effectiveness of cannabinoids are widespread; however, there are no well-developed RCTs, except DRE trials, in which children were included as study participants.(34, 84) Trials from 1980s have explored the safety and efficacy of pharmaceutical cannabinoids (nabilone and dronabinol) for CINV management in children.(141) Recently, there is also increase in retrospective reporting of medical cannabis data in children with ASD.(120)

Medical cannabis use in children is continuously evolving. Since the last decade, there have been a mounting number of studies on cannabinoid use in children.(84, 141-143) **Figure**

1.3. illustrates expanding studies on cannabinoid use in children. Medical cannabis has gained the attention of parents of children with complex health illnesses, including DRE, cancer, pain, and ASD.(84, 143) In a Canadian Pediatric Society (CPS) survey (2017), 419 out of 835 Canadian pediatricians reported having managed more than one child using cannabis for various medical reasons, 45 out of 204 of pediatricians managed five children or more.(144) Further, parents requested 316 out of 835 pediatricians to authorize medical cannabis for their children.(144) A cross-sectional survey conducted across Canada in 2020 reported that 92% of pediatric palliative care physicians and oncologists had provided care for children using cannabinoids for medical purposes (in the past 6 months) with and without authorization from a healthcare practitioner.(145) Parents use medical cannabis in their children, with or without authorization from their healthcare practitioners. (34, 36) In the past, cannabis-related societal stigma has limited research on its medical use. This resulted in parental and retrospective reporting of data related to cannabinoid use in children with complex health illnesses.(20)

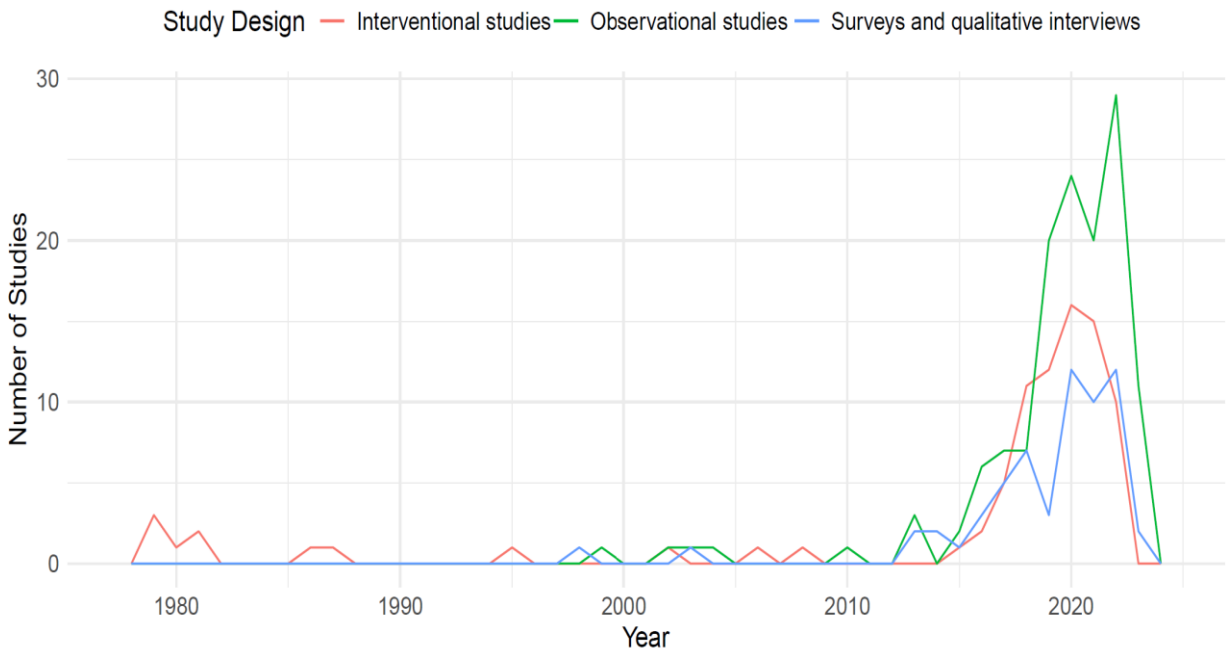


Figure 1.3. Studies included in the living systematic review reporting cannabinoids use for medical purposes in children.

1.8 Canadian Pediatric Society statement

In 2016, the Canadian Pediatric Society's (CPS) position statement reported insufficient evidence (most of the evidence was from case reports and series) informing the safety and efficacy of cannabinoid use for medical purposes in children and adolescents.(146) They urged hypervigilance while considering cannabinoids as a therapeutic option on a case-to-case basis in children due to possibility of harms. There is an increasing body of cannabis-related harm data from recreational cannabis use studies.(146) In CPS statement, they reported an urgent need for well-designed neuroimaging studies to evaluate the long-term safety of cannabinoids, including their effect on neuro-development outcomes in children. Since then, few RCTs related to purified CBD, THC and CBD-based products in children with DRE, were conducted .(84) In 2023, CPS updated its 2016 medical cannabis use in children statement.(34) They reported sustained tolerability and efficacy of CBD supported by long-term studies with a maximum of 2 years of

follow-up in children with Lennox-Gastaut syndrome.(146) They also reported that pediatricians should be prepared to have open discussions with parents of children on potential risks and benefits associated with cannabinoids used for medical purposes in children.(146) Additionally, they reported that pediatricians should tailor cannabinoid therapeutics to prevent harm, attenuate drug interactions, and monitor their efficacy in children.(146)

1.9 Safety considerations in children

Children receiving cannabinoids with complex health challenges, including DRE, cancer, and ASD, are on polypharmacy.(147) Polypharmacy is the prescription of ≥5 drugs as the course of treatment or for the management of any disease condition.(148) In Canada, 80% of medications are used off-label in children.(149) Most medications used in children are based solely on evidence from studies conducted in adults. Unlike adults, children have diverse age groups, including neonates, infants, toddlers, children, and adolescents;(150) these age groups have variable physical (metabolism, glomerular filtration rate, etc.) and pharmacokinetic profiles (clearance, bioavailability, etc.).(150)

Cannabinoids interact with co-administered drugs, especially CBD, and increase the risk of unintended effects and therapeutic failure either by increasing or decreasing the concentration of co-administered drugs. In CBD-related RCTs, the risk of developing adverse events in children was reported as 10% and greater than placebo.(151) Like adults, children have a different genomic makeup and possess pharmacogenomic variations, which predispose them to developing serious adverse events.(152) Pharmacogenomic variations are differences in the genetic makeup of individuals; they can impact both pharmacokinetic (how the body interacts with drugs) and pharmacodynamic responses (how drugs interact with the body), leading to variations in the safety and effectiveness of medications.(152)

1.9.1 Ethical considerations

There are several ethical considerations and barriers to studying the safety of cannabinoid use for medical purposes in children, including risk-benefit evaluation of cannabinoids, lack of health records linked to cannabis product dispensing, and diversity of pediatric age groups.(33) Children can not legally sign consent forms to participate in clinical research studies; therefore parents and caregivers' permissions are needed.(153) Informed consent requires open discussions with parents and caregivers on the potential risks and uncertainties of medical cannabis in children.(153) Children are diverse age groups with developing brain, impact of medical cannabis on brain development is unknown especially on neurodevelopment outcomes.(154) During adolescence, CB1 receptors are highly expressed across different regions of brain compared to adults. In recreational cannabis studies, THC exposures during adolescents has been associated with reductions in cognition, learning abilities and emotional response.(155) Chronic recreational cannabis use in children aged under 15 years has been linked with number of adverse effects including decreased ability to focus, suicidal ideation, suicide attempt, schizophrenia, decreased cognitive functioning and reduction in IQ levels.(156) Furthermore, recreational cannabis exposure in adolescents has been linked to changes in brain architecture, decrease in cerebral cortex, axons pruning, and synapse elimination.(155, 157) As a result, cannabinoids use for non-serious indications in children with developing brain in the absence of long-term neuroimaging data raises ethical concerns.

1.10 Drug-drug interaction considerations

Cannabinoids are metabolized by hepatic microsomal cytochrome p450 enzymes into more than 40 metabolites.(158, 159) CBD is hydroxylated by cytochrome (CYP) 2C9 and 2C19 at positions 4, 6, and 7 into primary metabolites: 6-hydroxy-CBD, 4-hydroxy-CBD, and 7-

hydroxy-CBD. Further, primary metabolites undergo glucuronidation by uridine 5-diphosphate-glucuronosyltransferase (UGT) 1A7, 1A9, and 2B7 at the phenolic oxygen position. (158) Metabolites are excreted from the body through feces and minimally via the renal route.(160) CBD possesses a substantial risk of interacting with other administered drugs in children.(100) CBD inhibits various microsomal enzymes: CYP1A1, 1A2, 3A4, 3A5, 3A7, 1B1, 2B6, 2C9, 2C19, and 2D6.(161-165) It inhibits phase 2 UGT enzymes 1A9 and 2B7.(161-165) In a preclinical study, CBD was reported to inhibit recombinant CYP2C19 and human liver microsomal (S)-mephenytoin 4'-hydroxylase activities with an IC_{50} of 8.70 at a 2.51 μM concentration.(161) CBD interacts with co-administered medications, including antiepileptics (clobazam, levetiracetam, and sodium valproate), mTOR inhibitors (everolimus and sirolimus), and antipsychotics (haloperidol).(100, 166-168) Children with refractory epilepsy and ASD often receive these medications, predisposing them to risk of adverse events.(169-174)

CYP 3A4 and 2C9 metabolize THC into 11-hydroxy-THC (the psychoactive form) and further undergo carboxylation into 11-carboxy-THC (non-psychoactive metabolite).(159, 160) Further, its non-psychoactive metabolite undergoes glucuronidation to get excreted from the body.(173, 174) The glucuronide form of 11-carboxy-THC is excreted through urine, while 11-hydroxy-THC is excreted predominantly through feces. Metabolites of THC undergo glucuronidation by enzymes: UGT1A1, 1A3, 1A8, 1A9, 1A10, and 2B7.(175)

THC also alters CYP450 enzymes; it inhibits CYP3A1, 1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, and 2J2.(176) When THC was co-administered with ketoconazole (CYP3A4 inhibitor), its bioavailability was increased by 27%, and its active metabolite 11-hydroxy-THC by 204%, resulting in CNS-related negative effects.(177) Further, when THC was administered

with rifampicin (CYP3A4 and 2C19 inhibitor), the Cmax of 11-hydroxy-THC was reduced by 87% and 36%.(177)

1.11 Pharmacogenomic considerations

Pharmacogenomics plays an integral role in understanding the safety of cannabinoids used for medical purposes in children.(178) Pharmacokinetic genomic variations predispose children to develop adverse events, either by increasing plasma levels of cannabinoids inside the body compartments or resulting in therapeutic failure by decreasing their plasma levels below the therapeutic window.(179) Pharmacogenomic variations may affect either pharmacokinetics, pharmacodynamics, or both of cannabinoids in children.(178) Pharmacodynamic variations may lead to reduced or excessive medication response.(180) Due to differences in children's genetic makeup, literature reports variability in cannabinoid response in terms of their dosing, safety, and efficacy.(178) However, the current literature is more focused on the effect of genomic variation on recreational cannabis use in the adult population.(178, 181)

In an observational study, patients with ABCB1, TRPV1, and UGT 2B7 polymorphism reported significant pain reduction with cannabis herbal formulation.(181) Furthermore, a significant number of patients with CNR1 genetic polymorphism dropped from the study due to a lack of pain reduction.(181) CBD has a variable response in controlling seizures in children with DREs; patients with the ABP1 rs12539 and AOX1 rs6729738 CC genotypes had significant seizure reduction, while children with the SLC15A1 rs1339067 TT genotype had non-significant seizure reduction.(182) In one case report, a 17-year-old adolescent with ASD with a null CYP 2D6 variant on CBD and fluoxetine suffered from serious adverse events (insomnia, agitation, yelling, and OCD symptoms); a potential interaction between CBD, fluoxetine, and CYP 2D6 was reported in this case.(178)

Purified CBD drug information leaflet lacks pharmacogenomic drug labeling.(151) With the emergence of new cannabis-based pharmaceutical products, it is necessary to understand how genetic makeup affects cannabinoid response in children in terms of dosing, safety, and efficacy. Applying pharmacogenomic principles will help to tailor the drug dosage regimen in children and achieve maximum efficacy by minimizing harm.

1.12 Rationale and research objectives

1.12.1 Rationale

Since ancient civilizations, cannabis has been used for medical purposes.(1) However, with recent changes in medical cannabis regulations, there is an increase in cannabis use for complex health illnesses management in children with or without authorization from healthcare practitioners.(34, 84) Canadian caregivers are aware of the potential benefits of cannabis in their children with seizures, ASD, and cancer.(120, 141, 183) Despite the increasing interest and research on using cannabinoids for medical purposes in children, there is a lack of literature on their long-term safety in children.(34, 146) Purified CBD and CHEs have shown promising results in managing DREs in children.(84) The growing use of cannabinoids for medical purposes demands a proper understanding of their metabolism and risk of interacting with other administered drugs. Pediatricians are reluctant to authorize cannabinoids in children due to a lack of clinical guidelines focused on their dosing, safety, and effectiveness in children.(144) Children with chronic conditions receive multiple drugs and cannabinoids, especially CBD, which interact with concomitantly administered medications and increase the risk of adverse events.(100) The increasing use of cannabinoids as adjuvant treatment in complex medication therapeutic regimens and a lack of long-term safety evidence necessitate a rigorous literature evaluation for safety signals.(34) There is a strong need to study the dosing and safety of cannabinoids used for

medical purposes in children to inform clinical practice. The main goal of this work is to investigate the safety of cannabinoids used for medical purposes in children.

1.12.2 Objectives

1. To study the available evidence on cannabis products' safety and dosing for various health conditions in children using a living systematic review (*Section 2.1*).
2. To evaluate the available evidence on cannabis products used for symptom management in children with cancer with regard to their safety, dosing, and reported benefits (*Section 2.2*).
3. To systematically appraise the current evidence on cannabinoids used for symptom management in children with ASD with regard to their dosing, safety, and reported benefits. (*Section 2.3*).
4. To summarize the adverse event profile of cannabinoids used for medical purposes in children from randomized controlled trials (*Section 2.4*).
5. To study the real-world safety profile of CBD in children using open pharmacovigilance databases and systematically review evidence on CBD-related clinical drug interactions in children (*Chapter 3*).

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Chapter 2 Evidence synthesis of available evidence

Section 2.1 Cannabinoids for medical purposes in children: A living systematic review

2.1.1 Overview

With ease in global medical cannabis regulations, both clinical research and interest in cannabinoid use for medical purposes in children has evolved rapidly. Cannabinoid use for medical purposes in children is an active research area. We felt a need to conduct a systematic review to comprehensively map the evolving evidence related to cannabinoid use (doses, types, formulations, route of administration, indications, safety, and reported benefits) for medical purposes in children, irrespective of indications and offer gaps in the evidence. This systematic review provides comprehensive, narrative, up-to-date evidence on the safety and reported benefits of cannabinoids used for various clinical indications in children.

This systematic review follows a living systematic review methodology; the current version is the opening version. The Clinical Pharmacology lab plans to update LSR every two years, many updated versions will be published beyond this version in the coming years.

Cannabinoids for medical purposes in children: A living systematic review

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2.1.2 Abstract

Aim We developed a living systematic review (LSR) that will continuously map safety and reported benefits related to the use of cannabinoids for medical purposes in children.

Methods We searched MEDLINE, Embase, PsycInfo, and the Cochrane Library from inception to April 2023. Studies involving at least one child <18 years who was administered plant-derived or pharmaceutical cannabinoids as an intervention or treatment for medical conditions were included.

Results Of 37,189 identified citations, 276 studies were included: 84 interventional, 131 observational, and 54 surveys and 7 qualitative studies. Among interventional and observational studies, common indications for cannabinoids in children were refractory epilepsy (n=146 studies, 188,726 participants), cancer treatment as well as symptoms experienced by patients with cancer (n=30 studies, 208,753 participants), and autism spectrum disorder (n=18 studies, 1285 participants). Common cannabinoids identified in interventional studies were purified cannabidiol (CBD) (78.6%, n=66 studies, 5235 participants) with a dose range of 2-50 mg/kg/day, tetrahydrocannabinol (6%, n=5 studies,148 participants) with a dose range of 2.5-10 mg/day (max dose of tetrahydrocannabinol in nabiximols was 32.4 mg) and nabilone (6%, n=5 studies, 267 participants) with dose range of 0.5-2 mg/day. In randomized controlled trials, purified Cannabidiol was reported to beneficial in reducing median seizure frequency ranging between 30-50%. Common adverse events (>20% of studies) in studies enrolling children were somnolence, diarrhea, vomiting, and decreased appetite.

Conclusion This LSR provides a comprehensive and current synthesis of evidence regarding the use of cannabis-based products for a variety of clinical indications in children and reveal knowledge gaps for future research.

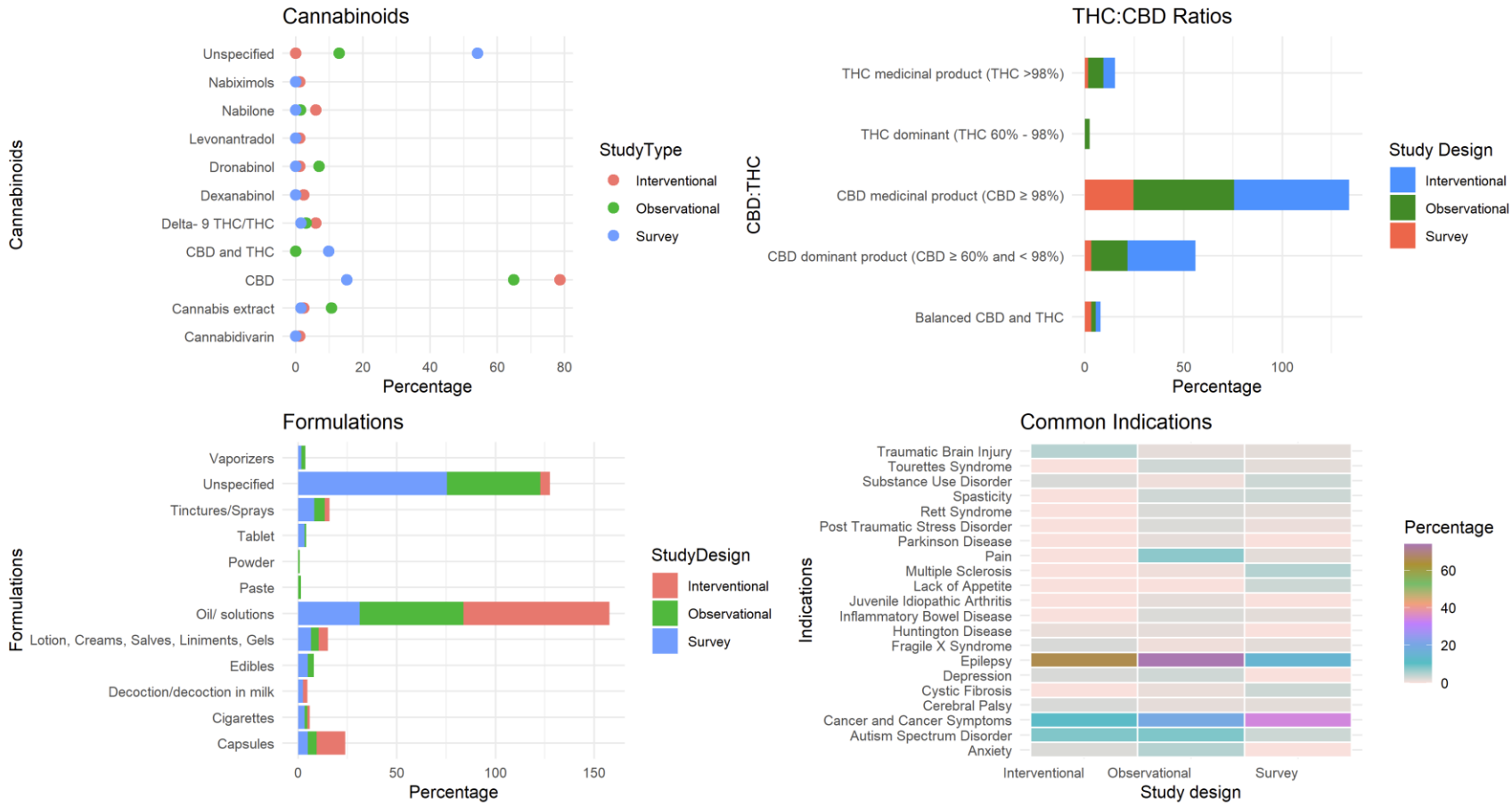
Keywords: Cannabinoids, medical cannabis; children; cannabidiol; refractory epilepsy; autism spectrum disorder; chemotherapy-induced nausea and vomiting; chronic pain; adverse events

Key Notes

- Cannabinoids are used for medical purposes in children with an expanding array of products and conditions studied, including drug-resistant epilepsy, autism spectrum disorder, symptoms experienced by patients with cancer, and various other health conditions.
- Purified CBD is the most studied cannabinoid in children with drug-resistant epilepsies.
- Knowledge gaps on the long-term cannabinoid-related adverse events, drug interactions, benefits, and tolerability of cannabinoids in children with medical complexities exist.

2.1.2.1 Graphical abstract

Cannabinoids for Medical Purposes in Children: A Living Systematic Review



2.1.3 Introduction

The cannabis plant has been used for medical purposes since ancient times.(1) In recent years, there has been a considerable increase in research on potential therapeutic applications of cannabis in both adults and children with refractory epilepsies, pain, and cancer.(2) In some countries, including Australia and Canada, authorizations permit the purchase of cannabis products for medical purposes in children.(3, 4) Families of children with complex health challenges are increasingly accessing cannabis-based products for epilepsy, autism spectrum disorder, cancer symptom management, and headaches.(4) For example, 92% of Canadian pediatric oncologists and palliative care providers reported caring for a child with cancer taking cannabinoids for symptom management in the past 6 months, despite limited studies in this population.(4)

In 2017, a systematic review reported a paucity of evidence supporting the use of medical cannabis in children.(5) Since then, research on cannabinoid use for medical purposes in children has markedly expanded, and many countries like Canada(6), Italy,(7) United Kingdom(8), and Australia(3) have initiated medical cannabis programs that include children. The landscape of cannabis-based products and populations using cannabis is evolving globally as more jurisdictions move towards legalization.(9) Although previous systematic reviews have touched on the safety and efficacy of cannabis in children,(5, 10) they have been limited to drug-resistant epilepsies (DREs) and have included interventional studies only.(10, 11) Recently, we published a systematic review and meta-analysis summarizing the safety profile of cannabinoids used as an intervention in randomized controlled trials for medical purposes in children.(12) A holistic perspective is required to ensure healthcare providers, public health mavens, patients, parents, and decision-makers have access to a comprehensive summary of the available evidence. Our

objective was to conduct a living systematic review on the use of cannabis-based products in children that will continue to comprehensively map the evolving evidence related to the use of cannabinoids (doses, types, formulations, route of administration, indications, safety, and reported benefits) for medical purposes in children.

2.1.4 Methods

The systematic review was registered with PROSPERO (registration number: CRD42020187433). We followed the preferred reporting items for systematic review and meta-analysis (PRISMA),(13) PRISMA-S guidelines,(14) Cochrane guidance for living reviews,(15) and Cochrane Collaboration(16) reporting items to ensure accurate and complete reporting. This review will follow a living systematic review methodology(15, 17) and run literature searches every two years to update the evidence base. Future iterations will be published on our website (medcannkids.ca) and held in an open-access repository (MedRxiv). They will also be submitted for publication in a peer-reviewed journal.

2.1.4.1 Eligibility criteria

The review included studies involving at least one child under 18 years of age who was administered either plant-derived cannabinoids or synthetic pharmaceutical cannabinoids by any route and dose as an intervention or treatment for any self-reported or diagnosed medical condition. Studies of all designs were considered, including randomized controlled trials (RCTs), such as parallel, factorial, crossover, cluster, pooled, adaptive, stratified, split-body, single-subject trials, quasi-experimental studies (non-randomized controlled trials, pre-post studies), and observational studies, including case-control, prospective or retrospective cohort series, uncontrolled cohort studies, case reports, case series, and cross-sectional studies. We excluded

editorials, expert opinions, review articles, and articles lacking data from primary sources. Additionally, we also excluded studies published in languages other than English or French.

2.1.4.2 Outcomes

The primary outcomes for this living systematic review were indications, types, doses, and formulations of cannabinoid used for medical purposes in children. The secondary outcomes were the safety and reported benefits of cannabinoids use for medical purposes in children. Further, secondary outcomes were operationalized based on available data across different identified study designs.

2.1.4.3 Search Strategy

The search strategy was designed with the assistance of an experienced health sciences librarian (ML) using a combination of subject terms and keywords related to cannabis (hemp, marijuana, cannabidiol, nabilone, tetrahydrocannabinol, epidiolex, sativex, nabiximols, and dexanabinol) and children or adolescents (preschool, infant, kindergarten, teenagers, and adolescent). Subsequently, the search strategy was peer-reviewed by another health sciences librarian using the Peer-Review of Electronic Search Strategies (PRESS) checklist to create extensive, robust, and comprehensive search strategy.(18) The search was conducted from inception to April 24, 2023 in four databases - MEDLINE (Ovid), Embase (Ovid), PsycInfo (Ovid), and the Cochrane Library (Wiley). Search results were restricted to human studies available in English or French only, without any restriction to study type or year of publication. A manual search and grey literature search including trial registries (WHO International Clinical Trials Registry Platform and ClinicalTrials.gov) were conducted to identify additional relevant studies. Finally, the search results were de-duplicated in the EndNote and uploaded to the

Covidence for screening.(19) The complete database search strategies are available in the **supplementary material** and via https://doi.org/10.34990/FK2/MV6CMP

2.1.4.4 Study selection and data extraction

Two reviewers (MC, AP, or OA) performed first-pass screening (title and abstract), second-pass screening (full-text screening), and data extraction. The senior author (LEK) resolved any disagreements among the reviewers that could not be resolved by discussion.

2.1.4.5 Data synthesis and analysis

A narrative synthesis of the extracted data was conducted using Microsoft Excel. The synthesis without meta-analysis (SWiM) guidelines for systematic reviews and Cochrane guidance for living reviews(15, 20) were followed. Given the diversity of included studies, no test for heterogeneity between studies, or meta-analysis on efficacy or safety was performed in this analysis. We did not account qualitative data analysis from qualitative studies for synthesizing findings. For safety outcomes, we considered the number of studies reporting the safety outcomes rather than the number of patients experiencing these outcomes.

2.1.5 Results

2.1.5.1 Search results and study selection

Of 37,189 identified citations, 276 unique studies were included: 84 interventional, 131 observational, and 61 survey and qualitative studies. **Figure 2.1.1.** describes the study selection process using the PRISMA flow diagram. The cumulative number of studies on medical cannabis including children substantially increased over the years, jumping from 13 studies in 2002 to 19 studies in 2010, followed by 170 studies in 2020 and reaching to 276 studies in 2023. Nine

interventional trials on cannabinoids for the prevention of the chemotherapy induced nausea and vomiting that include children were published between the years 1979-1995.

2.1.5.2 Characteristics of included studies

Characteristics of included studies varied broadly. **Table 2.1.1.** and supplementary **eTable 2.1.1.** presents detailed characteristics of interventional and observational studies related to cannabinoids used for medical purposes in children that were included in this review.

Interventional studies (n = 84) on cannabinoids used for medical purposes with children enrolled 7,767 participants. Most interventional studies were conducted in North America (48.8%, n=41), Europe (21.4%, n=18%) and Australia (15.5%, n=13). Trials were mostly single arm trials (71.4%, n=60) and randomized controlled trials (RCTs) (28.6%, n=24). Nearly half of interventional studies (44%, n=37) were registered with clinical trial registries, of which some (36.9%, n= 31) were registered with ClinicalTrials.gov. The median (IQR) number of participants in included interventional studies was 73 (31-111) in RCTs and 38 (18-93) in non-randomized trials. The median (IQR) duration of treatment in interventional studies was 12 (8-15.5) weeks, RCTs was 12 (6.25-14) weeks, which was similar to non-randomized trials which treated children for a median duration of 12 (11.7-22) weeks. Almost a third of interventional studies (30.9%, n=26) were blinded.

Observational studies (n=131) on cannabinoids for medical purposes that included children enrolled 267,028 participants. Observational studies related to cannabinoids used for medical purposes in children were conducted in North America (46.6%, n=61), followed by Europe (32.8%, n=43) and Asia (12.2%, n=16). Surveys (88.5%, n=54) and qualitative interviews (11.4%, n=7) related to use of cannabinoids for medical purposes in children were

conducted in North America (55.7%, n=34). In observational studies the most common design was described as chart review (26.7%, n=35), followed by cohort studies (16%, n=21) and cross-sectional studies (9.2%, n=12). The median (IQR) number of participants in chart reviews, cohort studies, and cross-sectional studies were 50 (21-108), 69 (27-91), and 918 (44-13931) participants, respectively.

2.1.5.3 Age group

Most interventional studies related to cannabinoids used for medical purposes included children from following age groups; 12-18 years (90.5%, n=76), 6-11 years (84.5%, n=71) and 2-5 years (75%, n=63). Similar patterns in age distribution were observed in observational studies, 12-18 years (70.2%, n=92), followed by 6-11 years (54.2%, n=71), and 2-5 years (42.7%, n=56). **Table 2.1.1.** compares different age groups across included studies.

2.1.5.4 Conditions for which Cannabinoids were Administered in Children

The most common diagnostic categories for which cannabinoids were administered to children for all the study designs included nervous system disorders, mental and behavioral disorders, and cancer. The most common indications for cannabinoids in children were drug-resistant epilepsies (DREs) followed by cancer and cancer symptom management, autism spectrum disorder, traumatic brain injury, cerebral palsy, and depression. Other indications included cannabis use disorder, headache, migraine, and low back pain. Supplementary **eTable 2.1.2.** details the identified indications of cannabinoids used for medical purposes in children.

2.1.5.6 Description of cannabinoids studied for medical purposes in children

Purified CBD was used in 78.6% (n=66) of interventional studies and 64.9% (n=85) of observational studies, followed by synthetic THC in 6% (n=5) of interventional and 3.1% (n=4)

of observational studies. Other cannabinoids included dronabinol, nabilone, cannabis extract, dexanabinol, cannabidivarin and nabiximols. While all observational studies described the cannabinoid contents, 12.9% (n=17) of observational studies do not clarify composition of cannabis components. **Table 2.1.2.** compares the different patterns of cannabinoids across the included studies.

The most common routes of cannabinoids' administration in children were oral, inhalational, followed by sublingual, topical and transdermal. The most frequently used cannabinoids' formulations were oral solutions, capsules, and tropical formulations (lotions, creams, salves, liniments, and gels). In 26.4% (n=52) of observational studies, surveys, and qualitative studies the formulation was not specified. A ratio of THC:CBD of 1:20 was most reported among the included studies. Based on the category of cannabinoids product, purified CBD (CBD ≥98%) was most commonly studied.(21) Cannabinoids in the included studies were given at a dose range: 2-50 mg CBD per kg/day,(22-29) and 2.5 mg to 10 mg or 18 mg/m^2 of THC(30-32) based on body surface area. In an interventional study, cannabidivarin, a minor phytocannabinoid was given at a dose range of 2.5-10 mg/kg/day.(33) Nabiximols, which contains a near equal ratio THC and CBD included a maximum dose of 32.4 mg/day and 30 mg/day, respectively.(34) Undefined cannabis herbal extracts (CHE) were used in 12.9% (n=17) observational studies with doses ranging from 0.6-20 mg per kg/day.(35) Dronabinol, a synthetic formulation of THC, was administered at a dose range of 2.2-9.1 mg/day in interventional studies and 0.7-25 mg/day in observational studies.(36-43) The dose range of nabilone, a different synthetic cannabinoid that acts as a THC analog, in interventional studies was 0.5-2 mg, (44-47) and its mean range in observational studies was 3.20-3.09 mg. (48, 49) Dexanabinol, a synthetic cannabinoid enantiomer which does not directly mimic THC, was administered as a

single-shot injection at a dose of 150 mg.(50, 51) The dose range of levonantradol, a synthetic derivative of THC was 0.5-1.5 mg in interventional studies.(52) **Table 2.1.3.** provides comprehensive information on dosing and frequency of cannabinoids in children.

2.1.5.7 Reported benefits of cannabinoid in children

In RCTs, purified cannabidiol was reported beneficial in reducing median seizure frequency by 30–50% compared to baseline in children with DREs (Lennox-Gastaut syndrome and Dravet syndrome).(23-27, 29) In single arm trials, purified CBD,(53-56) and CHEs(57-60) were beneficial in reducing seizure frequency (>50% reduction), duration, and severity.(50) Purified CBD was also used for the management of anxiety, depressive symptoms in children with refractory epilepsy.(61) CHEs in children with autism were used for psychomotor agitation, concentration, appetite, sleep disturbances, stereotype nature, and speech impairment.(62) In the RCTs, CBD was not beneficial in reducing aggressivity in children with ASD compared to placebo.(62) Interventional studies reported benefits of THC, and nabilone over commonly used antiemetics such as domperidone, prochlorperazine, and metoclopramide in controlling nausea and vomiting in children undergoing chemotherapy.(30-32, 38, 39, 44-48, 52, 63-70) Compared to the placebo, dexanabinol was not beneficial in improving the Glasgow outcome scale in children with traumatic brain injury;(50) however, there were reductions in intracranial pressure (<25 mmHg), cerebral perfusion pressure (<50 mmHg), and systolic blood pressure (<90 mmHg).(51) The supplementary **eTable 2.1.3.** lists the complete reported benefits of cannabinoid use in children by included studies.

2.1.5.8 Safety of cannabinoids in children

The most common cannabinoid-related adverse events (>20% of studies) in studies enrolling children were somnolence, diarrhea, vomiting, and decrease in appetite. The

supplementary **eTable 2.1.4.** provides further comparisons of safety event reporting. Other commonly reported cannabinoid-related adverse events reported by 10-20% of interventional and observational studies in children include pyrexia, fatigue, elevated transaminases, dizziness, nausea, pneumonia, sedation, irritability, and status epilepticus.

2.1.6 Discussion

In this review, we found that there is mounting literature on the use of cannabinoids for medical purposes in children with an expanding array of products and conditions studied including drug resistant epilepsies (DREs), autism spectrum disorder, symptoms experienced by children with cancer, traumatic brain injury (TBI), spasticity due to TBI, cerebral palsy, and various other health conditions. Purified CBD, nabilone, THC, dronabinol, dexanabinol, nabiximol, levonantradol, and CHEs were the most common cannabinoids used for medical purposes in children. These findings should be supplemented by indication-specific meta-analyses to inform benefits and safety measures and clinical care guidelines. This living systematic review will be updated frequently to help healthcare providers, patients, caregivers, research teams, and policymakers access evidence on the current use of cannabinoids for medical purposes in children.

This LSR providing comprehensive data on cannabinoid use for medical purposes in children is entirely different from our meta-analysis published elsewhere,(12) in terms of the number of studies (10 times more) and study designs of included studies. The analysis in the LSR is descriptive (only number, percentage, mean with SD/ median with IQR), mapping the expanding literature on cannabinoid use in children and comparing across observational, interventional, survey, and qualitative interview studies. In our included interventional studies, cannabinoids have been used outside of these approved indications to manage seizures in

developmental and epileptic encephalopathy, febrile infection-related epilepsy syndrome, fragile X syndrome, epileptic spasms (West syndrome), Lennox-Gastaut syndrome, Sturge-Weber syndrome, refractory epileptic encephalopathy, and infantile neuronal ceroid lipofuscinosis.(71, 72) We also found observational studies on cannabinoids in children with doose syndrome, epileptic Spasms (west syndrome), KCNT1-related epilepsy, and Rett syndrome. However, there were no clinical trials supporting their use in children with these indications. This may be related to the rareness of these conditions or lack of incentives for clinical trials to evaluate efficacy in a randomized control trials. CBD was also reported to be beneficial in managing seizures and other symptoms associated with tuberous sclerosis complex.(55)

Nabilone and dronabinol were more commonly used to prevent chemotherapy-induced nausea and vomiting in children with cancer, but children receiving dronabinol were reported to experience adverse events such as drowsiness and dizziness.(73) It is important to note that the use of these products in children is off-label. Studies reported the use of nabiximol and dronabinol in children with spasticity related to multiple sclerosis and cerebral palsy(34, 74), but there were no RCTs related to spasticity due to multiple sclerosis in children. These findings align with systematic reviews on cannabinoids in adults with spasticity.(75) CBD and THC may be helpful in managing symptoms related to autism, such as aggression, anxiety, irritability, and hyperactivity,(76) and have also shown promise in improving communication and sleep in this population.(35) There is a lack of supporting evidence on the beneficial effects of THC in reducing symptoms in children with Tourette syndrome and ADHD.(77)

Cannabinoid doses in identified studies including children varied based on type, formulation, and indication. CBD was administered at 2–50 mg/kg/day, while THC doses ranged from 2.5–10 mg or 18 mg/m². Nabiximols (THC:CBD ~1:1) had a maximum dose of 32.4

mg/day (THC) and 30 mg/day (CBD). Synthetic cannabinoids like dronabinol (THC) ranged from 0.7–25 mg/day, and nabilone from 0.5–3.2 mg/day. Dexanabinol was given as a single 150 mg injection. With all cannabinoids, trial duration remains a significant barrier to understanding the potential impacts on the developing brain. In single-arm trials of purified CBD, the maximum length of follow-up was up to 1 year, while in the observational study, the maximum follow-up duration for purified CBD was up to 2 years. None of the CBD-related CHE studies had a follow-up duration beyond 20 weeks.(57-60) Therefore, there is an urgent need for priority funding mechanisms to evaluate the long-term benefits and safety of cannabinoids used for medical purposes in children. Consistent with other systematic reviews, interventional studies reported more cannabinoid-related adverse events than observational studies,(5, 10) likely implicating an underreporting of events in observational literature. These adverse event findings are consistent with other systematic reviews.(78, 79) Commonly reported cannabinoid-related adverse effects include somnolence, diarrhea, vomiting, decreased appetite, sedation, seizures, fatigue, and elevated transaminase levels. (78, 79) CNS-related adverse events were associated with delta-9-THC, nabilone, and dronabinol. Parents and clinicians must conduct a risk-benefit analysis before considering cannabinoids for children, which is challenging to do if treatment-emergent adverse events are not well characterized.

2.1.6.1 Gaps in literature

Observational studies lacked information related to specific cannabinoids used, dosage form, frequency, and route of administration. Interventional studies investigating cannabinoids for medical purposes in children were limited to oral or sublingual routes of administration and formulations were limited only to oil or solutions. Included studies possess a challenge in calculating number of participants for specific indication because of overlapping reporting of

indications of cannabinoids. Real-world studies and pharmacovigilance efforts should provide complete information related to the route of administration, dosage forms and specific cannabinoid contents to better understand the safety and effectiveness of cannabinoids.

To improve the completeness of safety reporting, a guideline for research on cannabinoid interventions is warranted. Additionally, purified CBD was the most common cannabinoid used in clinical trials due to industry investment and marketing authorization. Given the complexity of the cannabis plant (such as the number of active compounds that are present including terpenes and flavonoids), purified CBD is unlikely to be directly comparable to CBD-enriched cannabinoid products available in different jurisdictions even when used at the same dose.

2.1.6.2 Strengths and limitations

The rigorous methods used in this living systematic review are a strength, including a registered protocol, comprehensive search strategy, independent screening, and data extraction to ensure the reliability and validity of the summarized evidence. The LSR is comprehensive and includes all study designs and cannabinoid product types This allows for greater flexibility to include studies on cannabinoid use in children and helped to generate reliable findings on the use of cannabinoids applicable over different indications in this initial report.

There are also several limitations to consider when interpreting our findings. A quality assessment of included studies was not performed since this qualitative synthesis focused only on types of cannabinoids, indications, and listing of cannabinoid-related adverse events. Given the heterogeneity of cannabinoids and populations studied, we did not pool adverse events or benefits of cannabinoid use in children in this report. Population and indication specific meta-

analyses are warranted to synthesize the data on adverse events and effectiveness across multiple cannabinoid product types.

2.1.6.3 Future directions

Although there is widespread use of cannabinoids in children, there is no uniformity in the dose, CBD THC ratio, type of cannabinoids, or how cannabinoid-related adverse events are reported. There are a lack of studies on the long-term safety and effectiveness of cannabinoids in children across the various indications for which medical use has been reported.(10) To fill this evidence gap, rigorous studies investigating the long-term safety and effectiveness of cannabinoids in children are needed across a wide range of therapeutic areas and populations. Questions related to rare adverse events, long-term safety, ability of cannabinoids to interact with other prescription drugs, and effects on children with comorbidities require further exploration.

2.1.7 Conclusion

Cannabinoids have been used in children for a variety of different health indications using various study methodologies. Knowledge gaps on long-term cannabinoid-related adverse events, drug interactions, efficacy, and tolerability of cannabinoids in children with medical complexities have been identified. Multicenter, multidisciplinary collaborations are needed to bridge evidence gaps by conducting innovative RCTs and real-world evidence studies that can be combined and contrasted across indications and jurisdictions.

2.1.8 Acknowledgement

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2.1.9 Author contribution statement

MC drafted the initial manuscript, acquisition, and interpretation of data, performed statistical analysis, critically reviewed and revised the manuscript for important intellectual content, and performed screening, data extraction, and critical revision of the manuscript for important intellectual content. MLL performed literature searches, data acquisition, study analysis, and critical revision of the manuscript for important intellectual content. LEK Conceptualized and designed the study, obtained funding, provided administrative, technical, or material support, critically reviewed and revised the manuscript for important intellectual content, and provided supervision. OA and AP performed screening, data extraction, and critically reviewed manuscript. YF critically reviewed and revised the manuscript for important intellectual content. HM critically reviewed and revised the manuscript for important intellectual content. RJH critically reviewed and revised the manuscript for important intellectual content.

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2.1.11 Figures

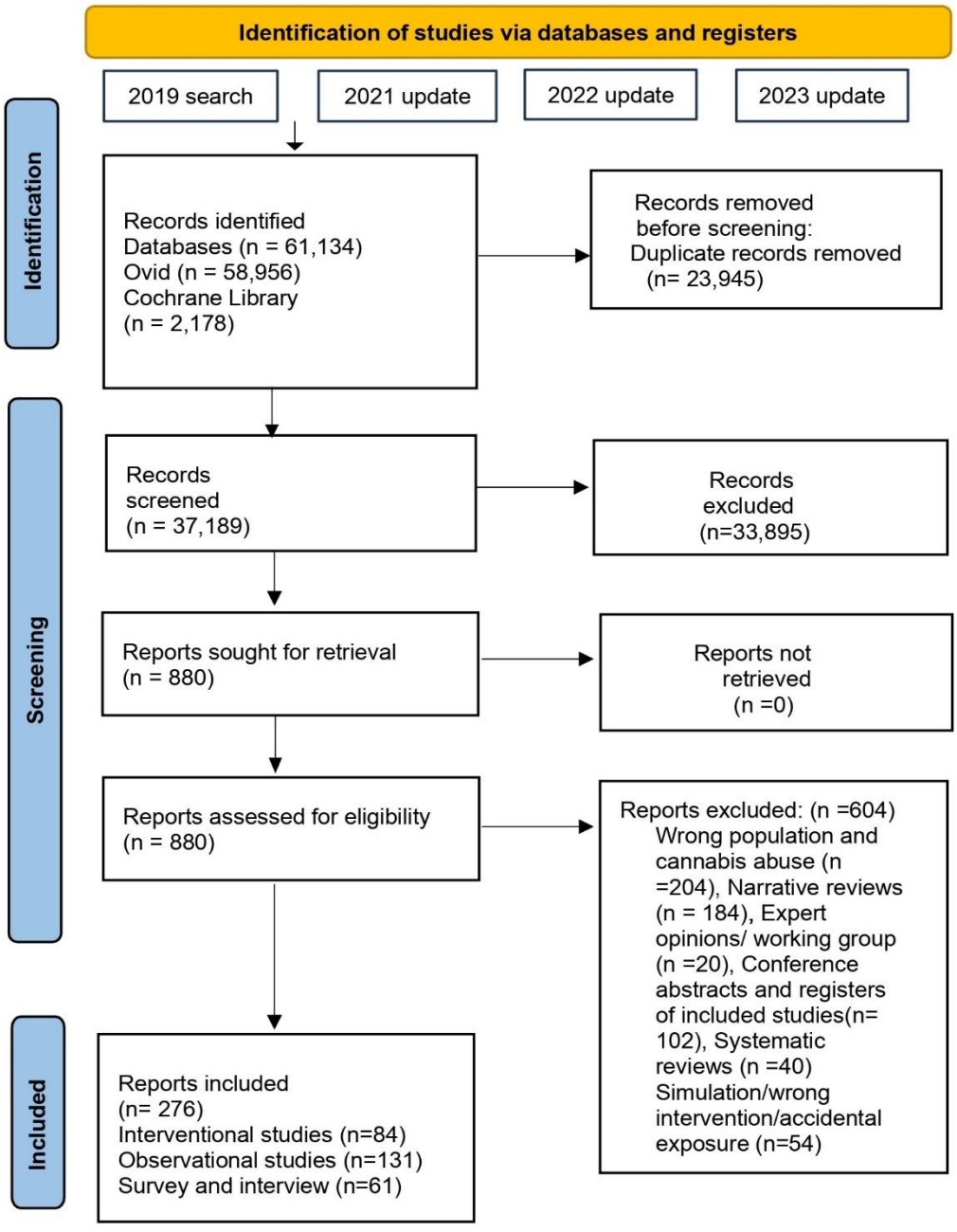


Figure 2.1.1. The PRISMA flow diagram of the studies included in the living systematic review.

2.1.12 Tables

Table 2.1.1. Characteristics of the included studies.

Variables	Interventional studies (n=84)	Observational studies (n=131)	Surveys and interviews (n=61)
Number of included participants			
Median (IQR) number of participants	45.3 (20-100)	18 (2-79.5)	103 (25.75-554.75)
Total number of participants enrolled	7,767	267,028	72,972
Number of studies that included pediatric age groups*			
Preterm neonatal births (prior to gestation)	2(2.4%)	4(3.1%)	2(3.3%)
Neonates (0-27 days)	3 (3.6%)	6 (4.6%)	5 (8.2%)
Infants (28 days- 1 year)	22 (26.2%)	21 (16%)	9 (14.8%)
Toddlers (13-23 months)	27 (32.1%)	29 (22.1%)	12 (19.7%)
Early childhood (2-5 years)	63 (75%)	56 (42.7%)	18 (29.5%)
Middle childhood (6-11 years)	71 (84.5%)	71(54.2%)	21 (34.4%)
Early adolescence (12-18 years)	76 (90.5%)	92 (70.2%)	33 (54.1%)
Late adolescence (19-21 years)	48 (57.1%)	41 (31.3%)	20 (32.8%)
Adults (over 21 years)	39 (46.4%)	34 (26%)	18 (29.5%)
Not reported	1 (1.2%)	14 (10.7%)	27 (44.3%)
Continents where participants were enrolled*			
North America	41 (48.8%)	61 (46.6%)	34 (55.7%)
Europe	18 (21.4%)	43 (32.8%)	15 (24.6%)
Australia/ New Zealand	13 (15.5%)	6 (4.6%)	8 (13.1%)
South America	11 (13.1%)	10 (7.6%)	1 (2.7%)
Asia	2 (2.4%)	16 (12.2%)	3 (4.9%)
Number of study centers			
Single centric	40 (47.6%)	96 (73.2%)	27 (44.3%)
Multi-centric	29 (34.5%)	11 (8.4%)	8 (13.1%)
Not reported	15 (17.9%)	24 (18.3%)	26 (42.6%)
Funding agency*			
Government	25 (29.8%)	12 (9.2%)	8 (13.1%)
Academic or research institutions	11 (13.1%)	9 (6.9%)	7 (11.5%)
Private	23 (27.4%)	16 (12.2%)	9 (14.8%)
Industry	53 (63.1%)	12 (9.2%)	2 (3.3%)
Unclear	1 (1.2%)	1 (0.8%)	NA

*Total will not add up to 100% because more studies met more than one category

Table 2.1.2. Description of cannabinoids used for medical purposes in the included studies.

Variables	Interventional studies (n=84)	Observational studies (n=131)	Surveys and interviews (n=61)
Types of cannabinoids in included studies			
Cannabidiol	66 (78.6%)	85 (64.9%)	20 (15.26%)
Cannabidivarin	1 (1.2%)	0 (0%)	0
Cannabis extract	2 (2.4%)	14 (10.7%)	1 (1.6%)
Delta- 9 THC/THC	5 (6%)	4 (3.1%)	1 (1.6%)
Dexanabinol	2 (2.4%)	0 (0%)	0
Levonantradol	1 (1.2%)	0 (0%)	0
Nabilone	5 (6%)	2 (1.5%)	0
Nabiximol	1 (1.2%)	0 (0%)	0
Dronabinol	1 (1.2%)	9 (6.9%)	0
CBD and THC	0	0	6 (9.8%)
Unspecified	0	17 (13%)	33 (54.1%)
Formulations of cannabinoids in included studies *			
Capsules	12 (14.3%)	6 (4.6%)	3 (4.9%)
Lotions, Creams, Salves, Liniments, Gels	4 (4.8%)	5 (3.8%)	4 (6.6%)
Oil/ solutions	72 (73.9%)	69 (52.6%)	19 (31.14%)
Edibles	0	4 (3%)	3 (4.9%)
Tinctures/Sprays	2 (2.4%)	7 (5.3%)	5 (8.2%)
Tablet	0	1 (0.8%)	2 (3.3%)
Cigarettes	1 (1.2%)	2 (1.5%)	2 (3.3%)
Vaporizers	0	3 (2.2%)	1 (1.6%
Unspecified	4 (4.8%)	62 (47.3%)	46 (75.4%)
Powder	0	1 (0.8%)	0
Paste	0	2 (1.5%)	0
Decoction/decoction in milk	2 (2.4%)	0	2 (2.4%)
Route of administration*			
Oral	72 (85.7%)	89 (67.9%)	17 (27.8%)
Inhalational/Smoked	1 (1.2%)	6 (4.6%)	11 (18.03%)
Topical	0	2 (1.5%)	7 (11.5%)
Transdermal	4 (4.8%)	0	0
Sublingual	2 (2.4%)	6 (4.6%)	1 (1.6%)
Intramuscular	2 (2.4%)	0	2 (2.4%)
Unspecified	3 (3.6%)	40 (30.5)	48 (78.6%)
Intravenous	2 (2.4%)	0	2 (2.4%)
Category of cannabinoids products * #			

CBD medicinal product (CBD ≥ 98%)	49 (58.3%)	67 (51.1%)	15 (24.5%)
CBD dominant product (CBD ≥ 60% and < 98%)	29 (34.5%)	24 (18.3%)	2 (3.2%)
THC medicinal product (THC >98%)	5 (6%)	10 (7.6%%)	1 (1.6%)
Balanced CBD and THC	2 (2.3%)	3 (2.3%)	2 (3.2%)
THC dominant (THC 60% - 98%)	0	3 (2.3%)	0

*Total will not add up to 100% because more studies met more than one category, # based on reported CBD:THC ratios using Therapeutic Goods Administration categories, Legends CBD Cannabidiol, THC Tetrahydrocannabinol

Table 2.1.3. Dosing and frequency of cannabinoid use for medical purposes in children.

Interventional studies (n=84)						
Cannabinoids	**Starting Dose Range**	**Maximum Dose Range**	**Frequency of cannabinoid administration**			
			BID	**TID**	**Other**	**Not reported**
Cannabidiol	2 mg/kg/day, 200 mg/day	50 mg/kg/day, 800 mg/day	47 (56%)	2 (1.2%)	0	17 (20.2%)
Cannabidivarin	2.5 mg/kg/day	10 mg/kg/day	1 (1.2%)	0	0	0
Cannabis extract	2 mg/kg/day	12 mg/kg/day	1 (1.2%)	0	0	1 (1.2%)
Delta-9 THC	2.5 mg/day, 10 mg/m^2	10 mg/day, 18 mg/m^2	0	0	3¥	0
Dexanabinol	48 mg/day	150 mg/day	0	0	2 (2.4%) $	0
Levonantradol	0.5 mg/day	1.5 mg/day	0	0	1 (1.2%) *	0
Nabilone	0.5 mg/day	2 mg/day	0	2 (1.2%)	2 (1.2%) #	0
Nabiximol	NA	THC: 32.4 mg/day, CBD: 30 mg/day	0	0	1 (1.2%) ##	
Dronabinol	2.2 mg/day	9.1 mg/day	0	1 (1.2%)	0	0
¥ study 1: every three hours in one study, study 2: 2 hours before the chemotherapy followed by 0, 4, 8, 16, 24 hours after the chemotherapy and study 3 every 6 hours; $ study 1 and study 2: single dose injection; * every four hours; #30 min before chemotherapy followed by every 6 hours; ## 12 sprays per day						
Observational studies (n=131)						
Cannabidiol	0.1 mg/kg/day, 50 mg/day	50 mg/kg/day, 600 mg/day	23 (17.5%)	3 (2.2%)	9 (6.8%) $	50 (38.1%)
Cannabis extract	0.6 mg/kg/day	20 mg/kg/day	2 (1.2%)	0	0	12 (9.1%)
Delta-9 THC	0.2 mg/day	12 mg/day	1 (0.8%)	0	3 (2.2%) ¥	3 (2.2%)
Nabilone	Mean (range)19 (3.20-3.09) mg/day	NA	1 (0.8%)	2 (1.2%)	2 (1.2%) #	1 (0.8%)
Dronabinol	2.5 mg/day, 2 mg/m^2,	0.7mg/kg, 25 mg/day	2 (1.2%)	0	0	7 (5.3%)
$ study 1: BID or TID, study 2: Two to three times a day, Study 3: 1st case: TID; 2nd case: BID, Study 4: QD, BID and TID, study 5: CBD oil (NR), CBD supplements (HS); sublingual spray (PRN), Study 6: Once daily, study 7: Q4D, Study 8 and 9: QID; **#** study 1 once daily, twice daily, **¥** study 2: three times daily; study 1: once a day, Study 2:QD, BD, TID, study 3: QD, BID **BID**: two times a day; **Q4H/QD**: every four hours, TID: three times a day						

2.1.13 Supplementary material

2.1.13.1 eTables

eTable 2.1.1. Detailed characteristics of the included interventional and observational studies.

Interventional studies (n=84)	
Study design	
Non-randomized controlled trial	60 (71.4%)
Randomized controlled trial	24 (28.6%)
Specific design	
Parallel	19 (22.6%)
Crossover	8 (8%)
Registered in a clinical trial registry	
Yes	37 (44%)
No	47 (56%)
Clinical trial registry name	
Australia and New Zealand Clinical Trials Register	4 (4.8%)
Deutsches Register Klinischer Studien (DRKS) German Clinical Trials Register	1 (1.2%)
German Clinical Trials Register	1 (1.2%)
ClinicalTrials.gov- The United States' Clinical Trial Register	31 (36.9%)
Randomized	
Yes	24 (28.6%)
No	59 (70.2%)
Unsure	1 (1.2%)
Blinded	
Yes	26 (30.9%)
No	54 (64.3%)
Unsure	4 (4.8%)
Who was blinded	
Participants	17 (20.2%)
Health care providers	13 (15.5%)
Outcome assessors	8 (9.5%)
Parents/caregivers	2 (2.4%)
Investigators	11 (13.1%)
Unclear	9 (10.7%)
Control group	
Yes	26 (31%)

Placebo	19 (22.6%)
Active	8 (9.5%)
Active control	
Prochlorperazine	4 (4.8%)
CBD and THC	2 (2.4%)
Stripentol and Valproate	1 (1.2%)
Domperidone	1 (1.2%)
Metoclopramide and Prochlorperazine	1 (1.2%)
Median (IQR) duration of treatment	
RCTs	12 (6.25-14) weeks
Non-randomized trials	12 (12-22) weeks
Total number of study participants treated	7,767 participants
Observational study design type (n=131)	
Case report	30 (22.9%)
Case series	23 (17.5%)
Cohort study	21 (16%)
Cross-sectional studies	12 (9.2%)
Treatment chart reviews	35 (26.7%)
Unclear	10 (7.6%)
Median (IQR) number of participants treated with cannabinoids	
Non-randomized trials	38 (18- 92) participants
Randomized controlled trials	73 (31- 111) participants
Cross-sectional studies	918 (44-13931) participants
Treatment chart reviews	50 (21-108) participants
Cohort study	69 (27-91) participants
Unclear study design	44 (11-133) participants
Case series	4 (3-6) participants
Surveys and interviews	
Cross-sectional surveys	54 (88.5%)
Qualitative interviews	7 (11.4%)

eTable 2.1.2. Different ratios and indications of cannabinoids used for medical purposes in children across the included studies.

ICD 10 diagnostic category (check-in all that apply)	**Interventional (n= 84)**	**Observational (n=131)**	**Survey and Interviews (n=61)**
Nervous System	67 (79.7%)	118 (90%)	46 (75.4%)
Congenital malformations, deformations, and chromosomal abnormalities	4 (4.8%)	0	3 (4.9%)
Injury, poisoning, and consequences of external causes	2 (2.4%)	1 (0.8%)	0
Mental and Behavioral Disorders	13 (15.5%)	24 (18.3%)	13 (21.3%)
Neoplasms (including oncology)	10 (11.9%)	19 (14.5%)	17 (27.9%)
Digestive System	1 (1.2%)	4 (3.1%)	1 (1.6%)
Blood, Blood-forming Organs, and Immune Mechanism	0	0	1 (1.6%)
Endocrine Nutritional and Metabolic Diseases	0	2 (1.5%)	3 (4.9%)
Circulatory System	0	1 (0.8%)	1 (1.6%)
Respiratory System	0	1 (0.8%)	1 (1.6%)
Skin and Subcutaneous Tissue	0	1 (0.8%)	1 (1.6%)
Musculoskeletal and connective tissue	0	3 (2.3%)	3 (4.9%)
Genitourinary system	0	0	1 (1.6%)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	0	8 (6.1%)	12 (19.7%)
Harmful effects of drugs, medicaments, or biological substances not elsewhere classified	0	1 (0.8%)	0
Unspecified	0	3 (2.3%)	0
Infectious and Parasitic Diseases	0	2 (1.5%)	2 (3.3%)
Detailed Indications (check-in all that apply)			
Anxiety	0	3 (2.3%)	3 (4.9%)
Autism spectrum disorder	7 (8.3%)	11 (8.4%)	3 (4.9%)
Traumatic brain injury	4 (4.8%)	2 (1.5%)	1 (1.6%)
Cancer and cancer symptom management including	9 (10.7%)	21 (16%)	23 (37.7%)

Chemotherapy-Induced Nausea and Vomiting (CINV)			
Refractory epilepsy	54 (64.2%)	92 (70.2%)	36 (59.1%)
Dysautonomic syndrome	0	1 (0.8%)	0
Epidermolysis bullosa	0	1 (0.8%)	1 (1.6%)
Fragile X syndrome	2 (2.4%)	1 (0.8%)	1 (1.6%)
Inflammatory bowel disease	0	3 (2.3%)	1 (1.6%)
Multiple sclerosis	0	1 (0.8%)	3 (4.9%)
Spasticity	0	4 (3.1%)	2 (3.3%)
Sturge-weber syndrome	2 (2.4%)	0	0
Post-traumatic stress disorder	0	3 (2.3%)	1 (1.6%)
Cannabis use disorder/ substance use disorder/ Crack abusers	2 (2.4%)	1 (0.8%)	2 (3.3%)
Huntington's disease	1 (1.2%)	2 (1.5%)	0
Cerebral palsy	2 (2.4%)	2 (1.5%)	1 (1.6%)
Depression	2 (2.4%)	4 (3.1%)	0
Tourette's syndrome	0	4 (3.1%)	1 (1.6%)
Juvenile idiopathic arthritis/ Arthritis	0	2 (1.5%)	0
Chronic pain including headache, migraine, and low back pain	0	10 (7.6%)	1 (1.6%)
Parkinson's disease	0	2 (1.5%)	0
Rett syndrome	0	3 (2.3%)	1 (1.6%)
Cystic fibrosis	0	1 (0.8%)	2 (3.3%)
Lack of appetite/weight loss	0	0	2 (3.3%)
Others	1 (1.2%) each**	1 (0.8%) each##	1 (1.6%) each^^
Reported ratios of THC: CBD (check-in all that apply)			
1:20	12 (14.2%)	8 (6.1%)	0
1:50	1 (1.2%)	1 (0.8%)	0
1:1	3 (3.6%)	3 (2.3%)	2 (2.4%)
3:5	1 (1.2%)	0 (0%)	0
1:6	1 (1.2%)	0 (0%)	0
<0.2%:93%	1 (1.2%)	0 (0%)	0
1:25	1 (1.2%)	2 (1.5%)	0
1:9	1 (1.2%)	2 (1.5%)	0
Others	0	1 (0.8%)	1 (1.6%)
1:15	0	(0%)	0
1:19	0	2 (1.5%)	0
1.44: 23.4	0	2 (1.5%)	0
1:2	0	2 (1.5%)	0
10% CBD, 0.1% THC	0	0	2 (3.2%)

Not reported	0	17 (12.9%)	56 (91.8%)
Country			
USA	48 (35.82%)	48 (36.6%)	24 (39.3%)
Australia	6 (4.48%)	6 (4.6%)	6 (9.8%)
Israel	10 (7.46%)	10 (7.6%)	1 (1.6%)
Spain	2 (1.49%)	1 (0.8%)	0
UK	3 (2.24%)	3 (2.3%)	1 (1.6%)
Canada	14 (11.19%)	13 (9.9%)	9 (14.8%)
Poland	1 (0.75%)	1 (0.8%)	0
Germany	14 (10.45%)	14 (10.7%)	4 (6.6%)
Italy	9 (6.9%)	9 (6.9%)	3 (4.9%)
France	3 (2.24%)	3 (2.3%)	0
Netherlands	1 (0.75%)	1 (0.8%)	3 (4.9%)
New Zealand	0 (0%)	0 (0%)	2 (3.3%)
Argentina	3 (2.24%)	4 (3.1%)	0
Sweden	0 (0%)	0 (0%)	0
Austria	1 (0.75%)	1 (0.8%)	0
Brazil	7 (5.22%)	6 (4.6%)	0
Switzerland	2 (1.49%)	1 (0.8%)	1 (1.6%)
Saudi Arabia	1 (0.75%)	1 (0.8%)	0
Denmark	2 (1.49%)	2 (1.5%)	0
Russia	1 (0.75%)	1 (0.8%)	0
Slovenia	1 (0.75%)	1 (0.8%)	0
Ireland	1 (0.75%)	1 (0.8%)	1 (1.6%)
Korea	1 (0.75%)	2 (1.5%)	0
Macedonia	1 (0.75%)	1 (0.8%)	0
Slovakia	1 (0.75%)	1 (0.8%)	0
Bologna	0	1 (0.8%)	0
Japan	0	1 (0.8%)	1 (1.6%)
Türkiye	0	1 (0.8%)	0
India	0	1 (0.8%)	0
Thailand	0	0	1 (1.6%)
Norway	0	0	1 (1.6%)
Belgium	0	0	1 (1.6%)
Eucador	0	0	1 (1.6%)
Mexico	0	0	1 (1.6%)

Others *3.4%: 6.39%, 0.03%: 23.5%, 1: 20, 1: 15, 1:10, 0.1: 100, <0.10%: 0.2%, 1:3, 5-8%: 7.5-12%, <1%: 9%, 1:14, 1:10, 1:10.6, <1:20, <1:16

* *ADHD, Obsessive compulsive, Oppositional defiant, Tics, Separation anxiety, General anxiety, Dup15q, and Doose syndromes, Neurogenetic syndrome, Constipation, Genetic generalized epilepsy, KCNT mutation related epilepsy, and Treatment resistant anxiety disorder.

ADHD, Obsessive compulsive, Oppositional defiant, Tics, Separation anxiety, General anxiety, Dup15q, Neurogenetic syndrome, Constipation, Genetic generalized epilepsy, KCNT mutation related epilepsy, Treatment resistant anxiety disorder, Developmental and

epileptic encephalopathy, Dravet syndrome, Epilepsy, unspecified, Febrile infection-related epilepsy syndrome, Infantile spasms, Intractable pediatric epilepsy, Lennox-Gastaut syndrome, Refractory epilepsy, Refractory epileptic encephalopathy, Doose syndrome, Drug-resistant epilepsy, West syndrome, and KCNT1-related epilepsy

^^Schizophrenia, Octahedra syndrome, Angelmen Syndrome, Developmental delays, Muscle spasms, Arthritis, Anorexia, Sleeping disorder, Gastrointestinal conditions, Neurological conditions, Glaucoma, Oncology, Neuropsychiatric, Pantothenate Kinase-Associated Neurodegeneration, HIV, Psychosis, Hypoxic encephalopathy, Bipolar disorder Sleep conditions, Arthritis, Aicardi syndrome, Atopic dermatitis, Tics, Ulcerative colitis/Crohn's disease, Agitation, and Mental health

eTable 2.1.3. Reported benefits of cannabinoid use for medical purposes in children in the included studies.

Author	Study design	Indications	Age of study participants, mean ± SD / median (range)	n (children if reported)	Cannabinoid	Reported benefits
			Interventional studies			
Heussler 2019	Non-randomized study	Fragile X syndrome	mean 10.4 (range 6-17) years	20	Transdermal CBD gel	Median reduction in anxiety depression, and mood score at 12 weeks compared to baseline −15.50 (−48.90%), PedsQL at 12 weeks 9.80 (16.70%), aberrant behavior checklist—community for FXS: social avoidance −3.00 (−66.70%), stereotypy −5.00 (−69.00%), socially unresponsive/lethargy −5.00 (−65.20%), Irritability −7.50 (−50.00%), hyperactivity −3.50 (−29.80%), inappropriate speech −3.00 (−44.40%), pediatric anxiety rating scale −6.00 (−38.20%), VAS hyperactivity−1.70 (−44.60%), tantrum −1.00 (−33.90%), anxiety −2.20 (−35.40%)
Chan 1987	Randomized double-blind cross-over trial	Chemotherapy Induced Nausea and Vomiting	mean 11.8 (range 3.5-17.8) years	30	Nabilone	Overall improvement in retching and nausea (nabilone vs prochlorperazine) 70% vs 30%
Abrahamov 1995	Non-randomized study	Chemotherapy Induced Nausea and Vomiting	mean 6.4 (range 3-10) years	8	delta-8-THC	Vomiting was completely prevented in all 8 children
Fairhurst 2020	Randomized controlled trial	Spasticity in children with cerebral palsy and traumatic brain injury	mean 12 years 4 months (range 8-18) years	72	Nabiximol (CHE spray)	No difference in spasticity on numeric rating scale (0-10) between nabiximol and placebo
Freeman 2018	Non-randomized study	Refractory epilepsy	median 10 (range 2-17) years	20	CBD	No data reported on benefits
Efron 2020	Randomized controlled trial	Intellectual disability and severe behavioral problems	mean 13.95 (range 8-16) years	8	Purified CBD (98%)	Reduction in ABC-I score in CBD group (mean reduction 12 points compared with 2.5 points) compared with placebo to baseline; Clinically significant (7.9 points in ABC-I) seen in 3 participants in CBD groups
Gaston 2019	Non-randomized study	Refractory epilepsy	Mean ± SD 19.5 ±12.9 years	132	Purified CBD	Significant reduction in seizures severity and frequency at 48 weeks compared to baseline, seizure severity (baseline vs 48 weeks):70.31±7.2 vs 22.46±5.9, seizure frequency (baseline vs 48 weeks) 177.08±83.9 vs 110.13±63.1

Gherzi 2020	Non-randomized study	Refractory epilepsy	range (2.5–23.2) years	10	Cannabis herbal extract (CBD: THC 5:3)	Significant correlations between THC and CBD total daily doses (mg/kg/day, with r=0.72 p<0.001, THC, r=0.74 p<0.001 for CBD); d) THC and CBD fractioned dosages of the previous evening (mg, with r=0.81 p<0.001 for THC, r=0.75 p<0.001 for CBD) and THC and CBD plasma concentrations (ng/mL) and volumes of decoction (ml/24 h, with r=0.75 p<0.001 for THC, r=0.65 p=0.002 for CBD) FM2 doses (mg/day, with r=0.75 p<0.001 for THC, r=0.65 p=0.002 for CBD),
Herlopian 2020	Non-randomized study (Epileptologist reading EEG was blinded)	Refractory epilepsy	mean 9 (range 2-16) years	9	purified CBD	Overall respond rates with CBD treatment after 2weeks and 1, 2, 3, 6, 9, and 12 months were 67%, 78%, 67%, 56%, 78%, 78%, and 78%
Kaplan 2017	Non-randomized study	Sturge-Weber Syndrome	mean 8.2 (range 2-19) years	5	purified CBD	At week 14 average seizure reduction frequency 43.2%
Mccoy 2018	Non-randomized study	Refractory epilepsy	mean 10.15 (2.1-17.8) years	20	Cannabis herbal extract (CBD: THC 50:1)	Median motor seizure reduction of 70.6% at 17-20 weeks, 50% responder rate of 63%, 50-90% seizure reduction rate: 9/20 (47%),>90% seizure reduction rate: 3/20 (16%), 100 seizure reduction rate 2/20 (10%), Quality of life childhood epilepsy score (baseline vs weeks 17-20) 31.58 (20.14) vs 50.00 (22.05), median seizure free days (baseline vs weeks 17-20) 11.89 (9.48) 18.32 (8.78)
Miller 2020	Randomized controlled trial	Refractory epilepsy (Dravet syndrome)	mean ±SD 9.3 ± 4.4 years	198	purified CBD	Reduction in convulsive seizure frequency from baseline: CBD10 48.7%, CBD20 group: 45.7% and placebo group: 29.8%, the percentage reduction from placebo: CBD10 29.8% (95% CI, 8.4%-46.2%; P= 0.01), CBD20 25.7% (95% CI, 2.9%-43.2%; P= 0.03)
Saft 2018	Open label interventional study	Huntington's disease	mean ±SD 28.3 ± 8.3	7	dronabinol	UHDRS motor score and the dystonia sub score (mean (sd), baseline to follow up) 70.9 (25.5) to 60.6 (26.9), dystonia sub score (mean (SD), baseline to follow up) 12.3 (4.0) to 8.0 (3.6)
Sands 2019	Open label interventional study	Refractory epilepsy	mean 9 (range 1-17) years	26	purified CBD	> 50% reduction in motor seizures 26.9%, seizure free 11.5%
Savage 2020	Open label interventional study	Refractory epilepsy	mean 15.5 (range 2.5–51) years	47	purified CBD	Mean percentage seizure reduction within first year CBD with Clobazam 58.5%, CBD alone 49.5%

Sharma 2019	Open label interventional study	Refractory epilepsy	mean ± SD 35.6 ± 16.4, (range 16-73) years	19	purified CBD	Repeated t-tests results for decreases in seizure frequency (baseline vs >10 weeks) 29.3 ± 39.4 vs 10.2 ± 16.8, [t(17) = 3.08, p = 0.0069], chalfont seizure severity scale (baseline vs >10 weeks) 70.5 ± 43.8 vs 14.3 ± 17.3, [t(17) = 5.77, p b 0.001], and Adverse event profile (baseline vs >10 weeks) 43.0 ± 13.4 vs 37.9 ± 12.7, [t(17) = 3.04, p = 0.0074], no changes in cortical thickness for baseline and follow-up visit (>10 week of CBD)
Szaflarski 2017	Open label interventional study	Refractory epilepsy	mean ± SD 12.3 ± 5.3 years	44	purified CBD	Mean reduction in raw seizure frequency 41.2 ± 112.4, positive linear correlation between CBD dosage range 5–50 mg/kg/day and CBD plasma level range 7.1–1200 ng/mL
Ekert 1979	Randomized double-blind cross-over trial	Chemotherapy Induced Nausea and Vomiting	median 11 (range 5-19) years	19	delta-9-THC	Study 1 episodes (THC vs metoclopramide) of nausea 6 vs 21, vomiting >6 episodes 2 vs 12, anorexia 4 vs 16, drowsiness 4 vs 2, study 2 (THC vs metoclopramide) nausea 3 vs 11, vomiting 1 vs 10, anorexia 3 vs 6, drowsiness 6 vs 0
Chang 1979	Randomized double-blind cross-over trial	Chemotherapy Induced Nausea and Vomiting	median 24 (range 15-49) years	15	delta-9-THC	THC had statistically significant benefit s for reducing episodes of vomiting and retching (<0.02), duration of nausea (<0.01), and volume of emesis (p<0.01) compared to placebo, reduction in nausea in TCH group 14/15 (93%)
Devinsky 2018a	Randomized controlled trial	Refractory epilepsy (Dravet syndrome)	mean 7.6 (range 4-10.9) year	34	purified CBD	CBD and its metabolites were reported to be dose-proportional (AUC0–t), CBD did not alter concomitant antiepileptic drug levels, except n-CLB
Barchel 2019	Open label interventional study	Autism Spectrum Disorder	median 11 (range 4-22) years	53	Cannabis herbal extract (CBD: THC 20:1)	Hyperactivity (n=38) (improvement 68.4%, improved: 68.4%, worsened 4.7%), sleep problems(n=21) (improvement 71.4%, worsened 4.7%), anxiety (improvement 47.1%, worsened 23.5%)
Maas 2006	Randomized controlled trial	Traumatic brain injury	range 16-65 years	846	Dexanabinol	Non-significant change in extended Glasgow outcome scale at 6 months (dexanabinol vs placebo) 50% vs 51%
Gray 2008	Non-randomized double-blind study	Cannabis use disorder	mean 18.8 (range 16-21) years	8	delta-9-THC	THC was associated with a good drug effect rating compared with placebo (<0.05) and there were no effects on the rating of bad drug effects in the THC group
Herman 1979	Randomized double-blind cross-over trial	Chemotherapy Induced Nausea and Vomiting	median 33 (range 15-74) years	113	Nabilone	Partial response (nabilone vs prochlorperazine) 81 (72%) vs 36 (32%), complete response (nabilone vs prochlorperazine) 9 (8%) vs 0
Libzon 2018	Open label interventional study	Motor disorder	mean 6.5 (range 1-16.8) years	25	Cannabis herbal extract (CBD: THC 20:1, 6:1)	Visit 1 vs visit 7: Barry Albright dystonia scale 15.68+6.23 vs 12.69+4.62, numeric rating scale dystonia 7.36+2.63 vs 6.40+2.68, NRS for spasticity 8.29+1.16 vs 6.60+2.43, gross motor function measure total 11.49+16.20 vs 14.71+15.06, quality of life 40 (0-80) vs 60 (20-80)

Knoller 2002	Randomized controlled trial	Traumatic brain injury	mean ± SD dexanabinol 31±13, placebo 29 ±12 years	67	Dexanabinol	Reduction in percentage time with intracranial pressure >25, cerebral perfusion pressure <50, systolic BP <90 mm Hg in dexanabinol p<0.005
Einhorn 1981	Randomized double-blind cross-over trial	Chemotherapy Induced Nausea and Vomiting	median 28 (range 15-74) years	80	Nabilone	Nabilone vs prochlorperazine: mean evaluation of nausea 1.1 vs 1.6, frequency of nausea 2.5 vs 5.08
Cronin 1981	Open label interventional study	Chemotherapy Induced Nausea and Vomiting	median 33 (range11-68) years	31	Levonantradol (THC)	Overall antiemetic response, complete response, or partial response 25/28
Devinsky 2017	Randomized controlled trial	Refractory epilepsy (Dravet syndrome)	mean 9.8 (range 2.3-18.4) years	120	purified CBD	Median percentage change in seizure frequency (range) (CBD vs placebo) -38.9 (-100 to 337) vs -13.3 (-91.5 to 230)
Devinsky 2018c	Open label interventional study	Refractory epilepsy (CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes)	range 1-30 years	46	purified CBD	Median percentage change in convulsive seizure frequency from baseline at week 12 51.4% (IQR 9-85%) (n=35), week 48 59.1% (IQR) 14-86% (n=27)
Devinsky 2018b	Randomized controlled trial	Refractory epilepsy (Lennox-Gastaut Syndrome)	mean 15.3 (range 2.6-43.4) years	225	purified CBD	Median percentage reduction in drop-seizure frequency from baseline CBD10 vs CBD20 vs placebo 37.2% vs 41.9% vs 17.2%
Pietrafusa 2019	Open label interventional study	Developmental and epileptic encephalopathy	mean 9.34 (range 1.9-16.3) years	29	purified CBD	≥50% reduction in seizure frequency 11/29, no patient reported worsening seizure frequency
Dalzell 1986	Randomized double-blind cross-over trial	Chemotherapy Induced Nausea and Vomiting	range 10 months - 17 years	18	Nabilone	Nabilone vs domperidone: mean no of vomits 5.94 vs 16.72, mean severity of nausea 1.50 vs 2.50
Thiele 2018	Randomized controlled trial	Refractory epilepsy (Lennox-Gastaut Syndrome)	mean 15.4 (range 2-55) years	171	purified CBD	Median percentage reduction in monthly drop seizure frequency from baseline CBD vs placebo 43.9% vs 21.8%
Sallan 1980	Randomized double-blind cross-over trial	Chemotherapy Induced Nausea and Vomiting	mean 32 (range 9-70) years	25	delta-9-THC	THC vs prochlorperazine: complete antiemetic response rate 39/79 vs 16/78, partial response 10/79 vs 15/78, no response 33/79 vs 47/78
Huntsman 2019	Open label interventional study	Treatment-resistant epileptic encephalopathy	range 1-10 years	7	Cannabis herbal extract (CBD: THC 20:1)	>25% reduction in seizure frequency 6/7, >50% reduction in seizure frequency 4/7

Gofshteyn 2017	Open label interventional study	Febrile Infection-Related Epilepsy Syndrome	mean 7.1 (range 3.9 to 8.5) years	7	purified CBD	Improvement in seizure frequency and duration in 6/7 children
Hussain 2020	Open label interventional study	Refractory epilepsy (Infantile spasms)	median 23 (range 19-36) months	9	purified CBD	1/9 patient responded to therapy, 8/9 did not show any improvement in clinical or electrographic responses
Thiele 2018	Open label extension study	Refractory epilepsy (Lennox-Gastaut Syndrome)	range 2-55 years	366	purified CBD	Median reduction in drop seizure frequency ranges from baseline 48-60%, mean monthly reduction in total seizure range frequency 48-57%
Devinsky 2016	Open label trial	Treatment-resistant epilepsy	mean 10.5 (range 1-30) years	214	purified CBD	Median monthly motor seizure reduction frequency 36.5% (0-64.7%)
Geffery 2015	Open label study	Refractory epilepsy	mean 11 (range 4-19) years	13	purified CBD	> 50% reduction in seizures, 9/13
Gaston 2019	Open label study	Refractory epilepsy	mean pediatric arm 10.4 (2-19) years	42	purified CBD	Change in serum plasma levels of clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine, no data on seizure control reported
Chen 2018	Open label study	Refractory epilepsy	mean 8.4 (range 1.6-16.6) years	40	purified CBD	Global impression of change assessment at 12 weeks very much/much improvement: 12/40, no data reported on seizure frequency
Szaflarski 2018	Open label study	Refractory epilepsy	mean 13.1 (0.4-62.1) years	607	purified CBD	≥ 50% reductions in seizures 52%, ≥ 75% reductions in seizures 31%, 100% reductions 11%
Rosenberg 2017	Open label study	Refractory epilepsy	median 11.7 (3.1-27.2) years	48	purified CBD	Quality of life in childhood epilepsy after 12 week of CBD treatment 8.2 ± 9.9-point improvement
Wheless 2019	Open label study	Refractory epilepsy	mean 7.6 (range 1 to ≤ 17) years	61	Synthetic CBD solution	No data reported on benefits , a bi-directional drug interaction occurred with cannabidiol and clobazam, mean plasma clobazam concentrations were 1.7- and 2.2-fold greater in patients receiving clobazam concomitantly with 40 mg/kg/day of CBD oral solution compared with 10 mg/kg/day and 20 mg/kg/day.
Szaflarski 2018`	Open label study	Refractory epilepsy	mean 10.1 ± 4.9 years	132 (pediatric (70) + adult (62))	purified CBD	Mean seizure frequency (baseline vs 48 weeks) 231.8 ± 535.0 vs 71.5 ± 177.25, mean seizure severity (baseline vs 48 weeks) 78.0 ± 62.8 vs 42.8 ± 38.4
Mitelpunkt 2019	Open label study	Refractory epilepsy	mean 9.1 ± 3.4 years	16	CBD enriched CHE (>93% CBD; <0.2% THC),	Reduction in seizure frequency at 12 weeks compared to baseline 81.9% and 73.4 ± 24.6%

Hess 2016	Open label study	Tuberous Sclerosis Complex	mean 14 (2-31) years	18	purified CBD	Median change in weekly seizure frequency after treatment of 4 months-48.8% (IQR -69.1% to -11.1%)
Laux 2019	Open label study	Refractory epilepsy	mean LGS/DS 12.8 (1.7–51) years, Other RE 13.3 (0.4–62.1) years	607	purified CBD	At week 12 ≥50% reduction in seizure frequency 53%, ≥75% reduction in seizure frequency 23%, 100% reduction in seizure frequency 6%
Aran 2021	Randomized controlled trial	Autism Spectrum Disorder	median 11.3 (range 5.1–20.8) years	150	CBD enriched CHE (167 mg/ml CBD and 8.35 mg/ml THC)	Disruptive behavior on the CGI-I very much or much improve 49% vs 21%, Median SRS Total Score (CBD versus placebo) 14.9 vs 3.6
BenMenachem 2020	Randomized controlled trial	Refractory epilepsy	mean 29.5 ± 10.5 years	34	purified CBD	No seizure reduction outcomes CBD increase in stiripentol exposure 17% increase in maximum observed plasma concentration, 30% increase in area under the concentration–time curve over the dosing interval [AUCtau]). concomitant CBD effect on valproate exposure 13% decrease in Cmax,
Freeman 2020	Randomized adaptive dose finding trial	Cannabis use disorder	range 16-24 years	48	Cannabidiol (99·9% purity)	Decreased THC-COOH: creatinine ratio by –94·21 ng/mL compared to placebo, increased abstinence from cannabis by 0·48 days per week range 0·15 to 0·82 compared to placebo
Gaston 2021	Open label study	Refractory epilepsy	pediatric arm 14.0 (9.9 ± 4.9) years	169 pediatric (89) + adult (80)	purified CBD	Seizure reduction 1 month 52%, 1 year 51%, 2 years 75% in children
Heussler 2020	Open label study	Autism Spectrum Disorder	mean 9.2 (range 3-17) years	37	Cannabidiol transdermal gel	At week 14: very much improved or much improved based on CGI-Improvement at 57% (n=37), mean Parent-Rated Anxiety Scale-ASD score improvement at week 14 46%
Iannone 2021	Open label study	Refractory epilepsy	median 3 (range 1-11) years	93	Cannabidiol	At least 50% reduction in seizure frequency compared to baseline at 12 month follow up 49% (n=51), 50.7% and 55.7 and 50% median reduction in total and convulsive seizures
Metternich 2020	Open label study	Refractory epilepsy	mean 16 (range 0-59) years	39, (26 children plus 13 adult)	Cannabidiol	no difference in cognitive decline after 3 months of CBD treatment, short-term/working memory were improved
Park 2020	Open label study	Refractory epilepsy	mean 10.4 (range 1.3 t0 18.8) years	47	Cannabidiol	Major seizure reduction range 54-72% and all seizure reduction range 61-70% compared to baseline

Poisson 2020	Open label study	Refractory epilepsy (KCNT1 mutations)	47 ,21, and 15 months	3	purified CBD and synthetic CBD	No notable benefits of CBD in the patients
D'Onofrio 2020	Open label study	Refractory epilepsy	mean 9 (range 6-14) years	125	purified CBD	Change in total seizure frequency from baseline was at month 1 −28.6% ± 36.1% at month 2, −37.4% ± 40.9%, and at month 6−41% ± 37.5%, > 50% reduction in seizures 28 (37.8%), ≥70% reduction in seizures 23 (31.1%), ≥90% reduction in seizures 6 (8.1%)
Thiele 2020	Randomized controlled trial	Refractory epilepsy (Tuberous Sclerosis Complex)	mean 11.4 (range1.1-56.8) years	224	purified CBD	Percentage reduction in the type of seizures from baseline CBD 25: 48.6% (95%CI, 40.4%-55.8%), CBD 50 47.5% (95%CI, 39.0%-54.8%), Placebo 26.5% (95%CI, 14.9%-36.5%) for the placebo group
Thompson 2020	Open label study	Refractory epilepsy	mean 7 (range10.6 ± 5.1) range	38	purified CBD	Mean change in Chalfont total score from baseline −25.72±62.2, no difference in baseline and follow cognitive and functional adaptive scores after 1 year of follow-up
Uliel-Sibony 2021	Open label study	Refractory epilepsy	mean 11.8 (range 1-37) years	92	CBD enriched cannabis herbal extract (CBD: THC 20:1)	Reduction in seizures <50% 30/92 (33.3%), 50–75% 26 (28.9%), 76–95% 15/92 (16.7%), Seizure free (>95%) 8/92 (8.9%)
Cáceres Guido 2020	Open label study	Refractory epilepsy (Epileptic Encephalopathy)	mean 10.2 (range 2.5-17.2) years	12	purified CBD	CBD administration was safe and well-tolerated except drug interaction with levothyroxine, no data reported on benefits
Anderson 2021	Open label study	Refractory epilepsy	median 10.4 (range 2–16) years	33	purified CBD	Median change in seizure frequency from baseline at month 3 -61.3% (n=33), at month 6 -62.9% (n=29), at 24 month -83.7%
Anderson 2020	Open label study	Refractory epilepsy	mean 19.3 (range 7-36) years	15	purified CBD	>70% reduction in seizure frequency 10/15 (67%), seizure free 6/15
Caraballo 2022	Open label study	Refractory epilepsy (Epileptic Encephalopathy)	mean 10.5 (range 2-17) years	59	purified CBD	>50% reduction in seizures 78% (n=59), ≥ 75% reduction in seizures 47.5% (n=59)
Davis 2021	Open label study	Refractory epilepsy	mean 20.96 ± 16.11 years	112 (51 adult plus pediatric 61)	purified CBD	> 50% reduction in seizure 56.3% (63/112), patient with following genes AOX1 rs6729738 CC: OR 6.69, and ABP1 rs12539: OR 3.96 were more likely to respond

Grayson 2021	Open label study	Refractory epilepsy	mean 7.3 (range 3-13) years	128 (64 pediatric plus 64 adults	purified CBD	Significant decrease in IED/minute in adult IDR 0.07, and non-significant in children IDR 0.87, mean change in seizure frequency at end of study compared with baseline -92.56 ± 315
Hurley 2022	Open label study	Refractory epilepsy (Rett syndrome)	median 12.6 (range 6-13.7) years	5	Cannabidivarin	Median reduction in seizure 79%, mean overall reduction in seizure frequency 3.3 to 7 seizure per month
Klotz1 2021	Open label study	Refractory epilepsy	mean 10.1 ± 0.86 years	35	purified CBD	Interictal epileptiform discharges (IED) baseline vs 3 months (36.8 ± 27.2 vs 19.6 ± 19.5), compared to baseline moderate correlation between IED reduction and percentage of seizure reduction
Madan Cohen 2021	Randomized controlled trial	Refractory epilepsy (Dravet syndrome)	mean 9.5 (range 2.2- 18.5) years	318	purified CBD	Median percentage reduction in convulsive seizure frequency: CBD10 41.2% (n=66), CBD 20 45.4 (n=128), placebo 21.7% (n=124)
Scheffer 2021	Open label study	Refractory epilepsy (Dravet syndrome)	median 9.3 (range 2.5–19.3) years	315	purified CBD	Median monthly reduction in seizure frequency compared to baseline at 12-week periods up to Week 156, convulsive seizures: 45%–74%, total seizures 49%–84%
Scheffer 2021 b	Nonrandomized Controlled Trial	Refractory epilepsy (Epileptic Encephalopathy)	mean 10.5±3.8 years	48	Transdermal Cannabidiol Gel	Monthly reduction in seizures 5 months vs 6.5-month 58% (−5.3%to 81.8%) vs 43.5% (−23.8% to 57.5%)
Thiele 2021	Open label study	Refractory epilepsy (Tuberous Sclerosis Complex)	mean 13 (1-57) years	199	purified CBD	Median reduction in seizure frequency at 12 weeks window across 48 weeks 54%-68%, ≥50-61% 53%, ≥75% 29-45%, 100% 6-11%, improvement in CGIC 87% of patients at 26 weeks
Szaflarski 2023	Open label study	Refractory epilepsy	median 11.8 (range 0.0–74.5) years	892	purified CBD	Median percentage reduction in total seizure 46-66%, convulsive seizures 50-67% compared to baseline, ≥50% reduction in seizure 51-59%, ≥75% 33-42%, and 100% reduction 11-17%
Berger 2022	Open label study	Treatment resistant anxiety	mean 21.1 (range 12-25)	31	purified CBD	At week 12 and 26 compared to baseline, mean (SD) change in Hamilton anxiety rating scale 20.5 (12), and -5.8 (9.6), overall anxiety and impairment scale -4.6 (4.2), and -2.7 (3.1), Quick inventory of depressive symptoms -3.5 (4.2), -0.6 (4.9), Social and occupational functioning scale +6.4 (8.9) and +1.3 (9.9)
Hacohen 2022	Open label study	Autism Spectrum Disorder	mean 9.2 (range2-25) years	82	CBD enriched cannabis herbal extract (CBD: THC 20:1)	Significant improvement in total Vineland scores M = 4.37, SD = 1.18, Sum(x) =332, $p < 0.001$, ADOS total calibrated severity scores M = −0.56, SD = .17, Sum(x) = 42, $p = 0.003$

Smegal 2023	Open label study	Sturge-Weber Syndrome	mean ± SD 13.10 ± 9 years 8 months	9	purified CBD	Mean vs follow-up Behavioral symptoms index 50.11 (±8.19) vs 54.22 (±4.21), Internal problems composite 46.22 (±7.17) vs 52.22 (±5.81), Emotional regulation index 51.22 (±12.29) vs 60.22 (±10.24), improvement in quality-of-life score 7/9
Stolar 2022	Open label study	Autism Spectrum Disorder	mean 10.7 (range 4.6, 5.25) years	59	CBD enriched cannabis herbal extract (CBD: THC 20:1)	Biochemical analysis results reported, Lactate dehydrogenase decreased compared to baseline 505.36 ± 95.1 IU/l, elevation in FT4 and TSH was also reported
Castellanos 2022	Open label study	Autism Spectrum Disorder	mean 11.3 (range 7-17) years	19	purified CBD	Significant improvement in CGI–S scores from pre- to post-treatment mean 4.68 ± 0.48 vs 3.95 ± 0.78
Berry-Kravis 2022	Randomized controlled trial	Fragile X syndrome	median 10 (range 3-17) years	212	Transdermal CBD gel	CGI ≥ 90% methylation group, ratings of "Very much improved," "Much improved," or "Minimally improved" (Placebo vs CBD 51.1% vs 37.7%), social avoidance treatment difference -0.39 ± 0.39, Irritability -1.74 ±1.20, lethargic -0.36 ± 0.70
Qiao 2021	Randomized controlled trial	Childhood constipation	Placebo 6.61±6 2.79, years Chinese herbal medicine 6.24 ± 2.20 years	200	Cannabis sativa herbal extract	Global symptom improvement (CHM vs placebo) 69% vs 42%, bowel movement per week 5.19 ±1.57 vs 4.02 ± 1.92
Silva 2022	Randomized controlled trial	Autism Spectrum Disorder	mean 7.68 (5-11) years	60	Cannabis herbal extract CBD: THC 9:1	Symptom outcomes (median ± SD, cannabis versus control) : Aggressivity 1.39±1.36 vs 0.81±1.05; Psychomotor agitation: 2.65±1.14 vs 1.64±1.28; Concentration: 2.96±0.86 vs 1.71±1.07; Meals: 0.38±0.82 vs 1.32±1.90, Sleep: 0.28±0.59 vs 0.77±1.61, Social interaction: 2.83±1.10 vs 1.68±1.01; 1.55, Anxiety: 2.90±1.23 vs 1.84±1.39, Stereotypy: 2.07±1.03 vs 1.45±1.06
			Observational studies			
Kuchenbuch 2020	Case series	SYNGAP1 developmental and epileptic encephalopathy	6, 7.5, 3.5 years	3	purified CBD	CBD reduced seizure frequency by >50% in all three children
Fleury-Teixeira 2019	Observational study	Autism Spectrum Disorder	mean 10.9±3.06 years	18	CBD-enriched Cannabis Herbal Extract	60% of patients showed improvement of ≥ 20% in attention deficit hyperactivity disorder; Behavioral Disorders, Motor Deficits, Autonomy Deficits, Communication and Social Interaction Deficit, Cognitive Deficits, Sleep Disorders and Seizures
Ponton 2020	Case report	Autism Spectrum Disorder	15 years	1	CBD-enriched Cannabis Herbal Extract	Patient experienced positive treatment effects on core social deficits and behavioral symptoms

Raz 2022	Case report	Autism Spectrum Disorder	17 years	1	Terpene-enriched CBD oil	Reduction in aggression, improvement in verbal capabilities, increase in fluency, spontaneous speech, and increased level of humor
Neubauer 2018	Observational study	Refractory epilepsy	median 8 (range 0.5-23) years	70	CBD >98%	Seizure free 14/66 (21.2%), > 90% improvement 7/66 (10.6%), 75-90% improvement 8/66 (12.1%), 50-75% improvement 3/66 (4.5%), 25-50% improvement 9/66 (13.6%), <25% improvement 10/66 (15.2%), no improvement 15/66 (22.7%)
Saade 2015	Case report	Refractory epilepsy (malignant migrating partial seizures in infancy)	10 months	1	purified CBD	Reduction in seizure frequency from10-20 per day to 5 per week, and of clinical seizure freedom up to 9 days
Laczkovics 2021	Case report	Substance abuse	16.9 years	1	Cannabidiol	Cessation of antidepressant medications with CBD and patient improve for depression, anxiety symptoms like phobias and symptoms of paranoia and dissociation, stopped abusing THC and no withdrawal symptoms
Jang 2022	Retrospective observational study	Refractory epilepsy (Lennox-Gastaut Syndrome)	median 5.5 (range 3.3- 25.3) years	30 (19 pediatric and 11 adult)	Cannabidiol	≥50 reduction in seizure 16/30, patient diagnosed with epilepsy at age were more likely to respond to therapy
Fernandez Cuerva 2022	Retrospective observational study	Refractory epilepsy	median 10 (2-16) years	31	purified CBD	Number of seizures was significantly reduced and caregiver's appreciation of effectiveness as good 14/31 (45.2%), and responded partially 7/31 (22.5%)
Anderson 2022	Case report	Autism Spectrum Disorder	17 years	1	CBD oil (>98% CBD) and CBD oil 50 mg CBD/ mL, <0.2mg THC/ml	CBD interacted with fluoxetine, patient suffered from insomnia, increased agitation, hyperactivity, vocal yelling, and worsening of OCD
Ma 2022	Case report	Autism Spectrum Disorder	9 years	1	CBD-enriched Cannabis Herbal Extract CBD: THC 20:1	CBD treatment was associated with reduction in self-injurious behaviors, negative behaviors, violent outbursts, and sleep disruptions.
Caraballo 2020	Cohort study	Refractory epilepsy	mean 10.5 (range 2-16) years	50	CBD enriched Cannabis Herbal Extract 95% CBD (CBD: THC 27:1)	80% (n=50) of children responded (decrease in seizure frequency) to CBD, median decrease in seizure frequency 299 to 102 (66% decrease), ≥ 50% reduction in seizure 73.5% (n=50), ≥ 75% reduction 49%, (n=50)

Carabal lo 2021	Case series	Refractory epilepsy (West syndrome)	mean 17 (10-12) months	8	CBD enriched Cannabis Herbal Extract (CBD: THC 25:1)	75–99% decrease in seizure frequency 2/8, 50–74% decrease in seizure frequency 2/8, < 50% decrease in seizure frequency 3/8, and no changes in seizure frequency 1/8
Singh 2020	Case report	Autism Spectrum Disorder and Lennox-Gastaut Syndrome	13 years	1	purified CBD	Improvement in seizure frequency and severity with CBD, but CBD increased plasma level of lithium
Rajara man 2018	Case report	Super-refractory status epilepticus	12 years	1	purified CBD	On day 12 of CBD, patients achieved clinical seizure freedom. CBD increased plasma levels of Clobazam and its metabolite
Koo 2020	Retrospective observational study	Refractory epilepsy	mean 5.1 (range 2.9-6.5) years	44	purified CBD	Reduction in seizure frequency in LGS 52.9 (n=34) at 3 months, 29.4 at 6 months (n=34), > 50% reduction in seizure frequency 3 (8.8%), <50% in 7 (20.6%) LGS patients, In DS complete seizure freedom 1/10, > 50% reduction in seizure frequency 2/10
Zilmer 2021	Retrospective cohort study	Refractory epilepsy	mean 10.6 (range 1.7-20.8) years	51	CBD enriched Cannabis Herbal Extract oil	≥50% reduction (n=54) in seizure at 3 months 31.1%, 6 months 31.4%, and 12 months 28.1%- and 24-months 20%
Nicoter a 2021	Case report	Williams–Beuren syndrome	13 years	1	purified CBD	CBD reduced seizure intensity, frequency, and improved social and motor skills
Warren 2017	Case series	Brain tumor related epilepsy	3 cases, 1 patient <18 years of age	1	purified CBD	On day 21 of CBD patient has reduction in seizure severity
Nowick i 2022	Case series	Refractory epilepsy	4, 12, 4, 13, and 5 years	5	CBD enriched Cannabis Herbal extract with THC	Improvement in seizure frequency and severity
Masata ka 2020	Case report	Refractory epilepsy (Infantile epileptic encephalopathy)	6 months	1	Artisanal CBD paste	By day 234 there was complete elimination of tonic clonic seizure frequency
Georgi eva 2023	Retrospective chart review	Refractory epilepsy	mean 20.3 (range 2-63) years	108	purified CBD	No data reported on benefits
Kühne 2023	Retrospective observational study	Refractory epilepsy	median 11.3 (range 0-72) years	311	purified CBD	After median observation period of 15.8 months, >50% reduction in seizures in 36.9% (n=311) of patients
Palmier i 2017	Retrospective observational study	Dysautonomic syndrome	range 12-24 years	12	CBD enriched Cannabis herbal extract	CBD significantly reduced body pain, physical component score, social role functioning in SF-36

Divisic 2021	Case series	Refractory epilepsy, chronic pain, and refractory spasticity	4, 5, 14,17, 18, 19 years	6	Cannabis herbal powers, 5–8% THC and 7.5–12% CBD	Cannabis powder was associated with reduction in seizure, and pain
Klotz 2019	Case series	Refractory epilepsy	10, 18, 20, 21, 54 years	5	purified CBD	CBD led to increase in plasma levels of brivaracetam by 95% to 280%
Tzadok 2022	Retrospective observational study	Refractory epilepsy	median age group 1: 7.7 years and group 2: 9.7 years	114	CBD enriched Cannabis herbal extract	Improvement in seizures frequency 84/114 (73.3%)
Barnett 2020	Retrospective medical record review	Tuberous Sclerosis Complex	mean ± SD 8.8±4.6 years	9	purified CBD	CBD treatment did not decrease in subependymal giant cell tumors and renal angiomyolipomas
Porcari 2018	Retrospective medical record review	Refractory epilepsy	mean age CBD 10.4 (1.1 to 18) years, CBD plus clobazam 7.8 (1.4 to 16) years, Clobazam 8.5 (1.4 to 18) years	210	Cannabidiol	CBD resulted in >50% reduction in seizures in 39% of patients and seizure free 10% of patients, CBD plus clobazam >50% reduction in seizure 44%, and seizure free
Borlot 2020	Cohort study	KCNT1-related epilepsy	mean age 40.8 months	27 (7 used CDB)	Cannabidiol	5/7 CBD kids showed marked improvement; 2/7 CBD kids showed minimal improvement
Coskun 2023	Case report	Refractory epilepsy	9 months	1	CBD enriched Cannabis Herbal extract	90% reduction in seizures reported
Tzadok 2016	Retrospective observational study	Refractory epilepsy	range 1-18 years	74	CBD enriched Cannabis Herbal extract (CBD: THC 20:1)	Reduction in seizure frequency: 66/74 (89%), 75–100% reduction 13/74 (18%), 25–50% reduction 9/74 (12%), <25% reduction 19/74 (26%)
Klier 2020	Case report	Anxiety in Crohn's disease	14 years	1	CBD capsules	CBD improved anxiety symptoms to patient including symptoms of needle phobia, fear of medical interventions, and social phobia as reflected by change in CGI-S score but no remission the anxiety scores
Wiemer-Kruel 2019	Case report	Tuberous Sclerosis Complex	6.5 years	1	CBD solution	CBD increase plasma concentration of everolimus, patient failed to respond to CBD
Herlopian 2022	Retrospective observational study	Refractory epilepsy	18 months to 52 years	52	purified CBD	EEG was improved in 32/46 (70%) of patients and worsened in 3/46 (7%) of patients

Paprocka 2021	Case report	Refractory epilepsy (Lennox-Gastaut Syndrome)	11 years	1	purified CBD	CBD add-on reduced seizures frequency in the patient
Bolsoni 2019	Case report	Post-traumatic stress disorder	15 years	1	Cannabidiol	CBD did not have any effect on preventing PTSD
Savage 2020	Retrospective observational study	Refractory epilepsy	range 2.5-51 years	47	Cannabidiol	Mean reduction in seizure frequency (at best point year 1) CBD+ Clobazam vs CBD alone 58.5 vs 49.5
Prakash 2020	Case report	Refractory epilepsy (Lennox-Gastaut Syndrome)	9 years	1	purified CBD	Complete control of seizure and near normalization of EEG
Patel 2021	Retrospective medical record review	Refractory epilepsy	median 13 (range 1-51) years	54	purified CBD	> 50% reduction in seizures 20/54 (41.7%), no reduction in seizure frequency 14/54 (29.2%), seizure responder rate 1.7%–42.6%
Marchese 2022	Retrospective observational study	Refractory epilepsy	median 16.1 (range 2-54) years	37	CBD enriched Cannabis herbal extract (CBD 24%)	Seizure free 7/37 (19%), > 50% reduction in seizures 27 (73%), < 50% improvement 2/37 (5%)
Riva 2023	Retrospective observational study	Refractory epilepsy	median seizure onset age 5 months	6	purified CBD	5/6 (83%) very good responders, 1/6 (17%) partial responder
Cohen 2022	Retrospective medical record review	Refractory epilepsy	mean 10.1 (range 3-20) years	42	purified CBD and artisanal CDB	Overall seizure outcome artisanal vs pharmaceutical 0 (−50 to 50) vs −50 (−90 to 0)
Poisson 2020	Case series	Refractory epilepsy (KCNT1 mutations)	47, 21, 15 months	3	purified CBD	No response to CBD 2/3, reduction in seizure intensity 1/3
Fetta 2023	Case series	Refractory epilepsy (FIRES)	4, 6 years	2	purified CBD	Both the patients became seizure free after 1 year of CBD therapy
Pane 2020	Case series	Refractory epilepsy	4,15, 18, 21 25 years	5	Medical grade cannabis	Upon CBD treat all of 5 patients reported reduction in seizure frequency, and improvement in severity, mood, and sleep
McNamara 2020	Retrospective medical record review	Refractory epilepsy	mean 9.8 (range 1.2-19.8) years	87	purified CBD	One-third of the patients on CBD and valproate developed thrombocytopenia (9/87)
Abu-Sawwa 2022	Retrospective cohort study	Refractory epilepsy	mean 15.2 years	100	purified CBD	Seizure related hospitalization before CBD versus after CBD 23 VS 15

Villanueva 2022	Retrospective observational study	Refractory epilepsy	mean 15.9 (range 0.9–58.2) years	102	purified CBD	reduction in seizure severity 33/54 (61.1 %), unchanged seizure severity 17/54 patients (31.5 %), median number of total seizures 47.6%, seizure freedom at 1-month 6/79, 3/54 (5.6 %) at 12 months, and 6/99 (6.1 %) at last visits of patient
Lala 2022	Case report	Refractory epilepsy (Febrile Infection Related Epilepsy Syndrome)	7 years	1	Cannabidiol	NA
Potey 2022	Case series	Refractory epilepsy	median 6 years	4	purified CBD	CBD increased plasma levels of Clobazam, no data on benefits reported
Li 2016	Case series	Cancer	2 and 4 years	2	THC and CBD oil drops	THC CBD oil drops were associated with hypotension, no data reported on efficacy
Kalaba 2022	Observational study	Multiple indications (pain, insomnia, Parkinson disease, migraine, Alzheimer's disease, epilepsy, CINV, spasticity, Insomnia and PTSD)	mean 57.2 (range 9-94) years	535	Multiple CBD THC products including CBD: THC 1:1, CBD dominant products, and THC dominant products	After cannabis initiation there was reduction in medications after 1 year compared to baseline, antidepressant reduction 19.3%, opioids 2.6%, NSAIDs 18.8%, and benzodiazepines 16.4%
Appendino 2019	Case report	Refractory epilepsy (Nexmif Gene KIAA2022)	15 years	1	purified CBD	No benefits reported (seizure reduction)
Zawar 2021	Case series	Refractory Epilepsy (Jeavons Syndrome)	20 and 14 years	2	purified CBD	CBD was associated with eyelid myoclonia in patients with Jeavons Syndrome
Shlomovitz 2021	Cohort study	Tuberous Sclerosis Complex	median 15.6 years	91	purified CBD, CBD-enriched Cannabis Herbal Extract (CBD: THC 20:1)	No difference in response rate among three groups vagus nerve stimulation, CBD-based products, and the ketogenic diet with a response rate of 30-40%
Livezey 2022	Retrospective cohort study	Neurological indications	NA	136	Cannabidiol	65 drug-drug interactions were reported and 58, (89%) were due to clobazam
Duma 2019	Prospective observational study	Refractory epilepsy	NA	17	purified CBD	50–80% seizure reduction 5/17 (29%), intermittent reduction of seizure frequency 3/17 (18%), no response in seizure reduction 5/17 (29%)

Whitney 2021	Case series	Refractory epilepsy (15q13.3 microdeletion syndrome)	median 12 (3-15) years	13	Cannabidiol	CBD was used in 2 patients, but no change in seizure frequency
Celario 2022	Observational study	Refractory epilepsy	NA	15	purified CBD	No results reporter only study design reported
Manivannan 2023	Retrospective medical record review	Refractory epilepsy	range 6-16 years	26	Cannabidiol	26% reported improvement in quality of life, 19% reported improvement in seizure, 23.8% reported worsening of seizures
Erridge 2022	Case series	Refractory epilepsy	mean 9.7 ±4.5 years	39	CBD isolate oils, CBD broad-spectrum oils, and CBD, THC combination therapy	50% reduction in seizure frequency 25/35 (65.7%)
Wieckiewicz 2022	Cohort study	Depression	mean 33.7 (range 16-69)	90	Cannabidiol	No data reported on benefits
Gregorčič 2022	Retrospective observational study	Refractory epilepsy	mean 6.2 (range, 1.3–17) years	131	Cannabidiol	1 patient reported CBD, no data on benefits reported
Olson 2021	Cohort study	Refractory epilepsy (CDKL5 deficiency disorder)	mean 8.1 (8 months- 39) years	177	FDA approved and non-FDA approved CBD	3 months seizure response FDA regulated CBD 3/19 (21%), non-FDA regulated CBD 2/18 (50%), worsening seizures FDA regulated CBD 4/19 (29%), non-FDA regulated CBD 1/18 (25%)
Marusak 2023	Observational study	Refractory epilepsy	mean 12.73 ± 5.2 years	11	Cannabidiol	90% participants reported reduction in seizure and 60% reported reduction in anxiety symptoms
Vicino 2022	Retrospective observational study	Refractory epilepsy	mean 38 (range 15-57) years	35	Cannabidiol	Responders (>30% reduction) 7/35 (35%), super responder (>80% reduction) 4/35 (20%)
Bar-Lev Schleider 2019	Retrospective observational study	Autism Spectrum Disorder	mean 12.9 ± 7 years	188	CBD enriched Cannabis Herbal Extract (CBD: THC 20:1), 3% THC oil	28/ 188 (30.1%)0.1%) reported significant improvement, 50/188 (53.7%) moderate, 6/188 (6.4%) slight and 8/188 (8.6%) had no change in their condition.
Szaflarski 2017	Observational study	Refractory epilepsy	mean 12.9 (range 1-62) years	80	purified CBD	Patient treated with CBD 76% of them had high income of $40,000+/year, 13% experienced food scarcity, 8% were not able to afford antiepileptic drugs, no data reported on benefits

Malaca 2021	Observational study	Refractory epilepsy	mean 8.7 (range 3-26) years	9	Cannabidiol	Serum levels of CBD, 7-OH-CBD) and 7-COOH-CBD were higher in patients treated with Epidiolex CBD compared to other formulations, no reported data on seizure reduction
Carabal lo 2022	Retrospective medical record review	Refractory epilepsy (epileptic spasm)	mean 10.5 (range 2-15) years	21	Cannabidiol	1/21 patients were treated with CBD and responded well
Prager 2022	Case series	Refractory epilepsy (Rasmussen encephalitis)	8, 13, and 14 years	3	purified CBD	CBD was efficacious in reducing seizures in all the 3 patients
Wang 2020	Observational study	Refractory epilepsy	mean 9.7 ±4.3 years	29	CBD enriched Cannabis Herbal Extract	Median peak CBD concentration 13.1 (IQR 6.8–39.3) ng/mL, median time to peak 2 (2-4) hours, interaction between zonisamide and levetiracetam
Aran 2018	Retrospective observational study	Autism Spectrum Disorder	mean 11.8 ± 3.5 years	60	CBD enriched Cannabis Herbal Extract (CBD: THC 20:1)	Global impression of change in behavior, anxiety and communication much improved or very much improved 61%, improvement in anxiety 39%, communication 47%
Crippa 2016	Case series	Refractory epilepsy	10 and 7 years	2	CBD enriched Cannabis Herbal Extract	CBD enriched Cannabis herbal extract without THC improved seizures in both the patients
Failing 2021	Medical record review	Juvenile Idiopathic Arthritis	mean 29.7 ± 8 years	136	Cannabidiol	47/136 (34.5%) showed no interest in using CBD, 79/136 (54%) contemplating using CBD
Shanno n 2016	Case report	Posttraumatic Stress Disorder	10 years	1	Cannabidiol herbal extract	CBD administration increases sleep quality, quantity, and reduced anxiety of patient
Ebrahi mi-Fakhari 2020	Retrospective observational study	Tuberous Sclerosis Complex	median 17 (range 3-45) years	25	Cannabidiol	Rapamycin inhibitor levels were higher in 76% patients receiving CBD, median change in everolimus from baseline +9.8 ng/mL, sirolimus +5.1 ng/mL
Tartagli a 2019	Case series	Fragile X syndrome	3.5, 26, and 22 years	3	Cannabidiol	All the 3 patients, there was reductions in social avoidance, anxiety, improvements in sleep, motor coordination, language skills, feeding and sensory processing
Choi 2020	Case report	Epidermolysis Bullosa	13 years	1	CBD enriched Cannabis Herbal Extract, Dronabinol	Pain and nausea were successfully managed in patient with epidermolysis bullosa
Oliveir a 2020	Case report	Zellweger syndrome	1 year and 9 months	1	Cannabidiol	92% reduction in total seizure frequency after CBD administration
Bonard i 2023	Case report	Refractory epilepsy (FIRES)	14 years	1	Cannabidiol	After CBD administration, regained complete consciousness and became seizure free for 8 months after 1 year of follow up

Hausman-Kedem 2018	Observational study	Refractory epilepsy	mean ± SD 9.6 ± 4.9 years	46	CBD enriched Cannabis herbal extract (CBD: THC 20:1)	Seizure reduction range 0-49%, 50–75% seizure reduction 10/46 (22%), 75–99% seizure reduction 14/46(30%), seizure free 2/46 (4%)
Madden 2020	Case report	Cancer	13 years	1	Cannabidiol	Cannabis increased plasma levels of methadone by 271 ng/mL
Nowicki 2018	Case series	Refractory epilepsy	4, 12, 4, 13, and 5 years	5	CBD enriched Cannabis Herbal Extract	THC added cannabis herbal extract formulations were beneficial in children not responding to CBD extracts alone
Knupp 2019	Prospective observational study	Refractory epilepsy	median 10.3 (IQ range 6.8–12.6) years	21	Oral cannabis extract	Observed response rate (>50% seizure reduction) 5/21 (24%), increase in seizures 3/21 (14%)
Treat 2017	Retrospective medical record review	Refractory epilepsy	mean 7.5 (range 0.6-18) years	119	Oral cannabis extract	Some improvement in seizures 58/119 (49%), > 50% reduction in seizures 29/119 (24%)
Hasan 2010	Case report	Tourette syndrome	15 years	1	THC	Improvement in YGTSS score from 97 to 54, GTS-QOL score, 54 to 21, and decrease in ADHD symptoms CTRS-R: L score from 53 to 47
Lorenz 2002	Case report	Neuronal ceroid lipofuscinosis	3 years and 4 months	1	Dronabinol	THC was reported to be beneficial in reducing seizures and improving overall health
Kuhlen 2016	Retrospective observational study	Spasticity	median 12.7 (range 1.3- 26.6) years	16	Dronabinol	Dronabinol was safe, tolerable, and efficacious in reducing symptoms of spasticity at dose range of 0.08 to 1.0 mg/kg/d, median dose of 0.33 mg/kg/d
Rower 2021	Retrospective medical record review	Cancer	median 12.5 (range 6–17) years	10	Dronabinol	Range of THC concentrations 0.100 and 0.128 ng/mL, no data reported on benefits
Elder 2015	Retrospective medical record review	Cancer	mean 13.9 ± 3.2 years	66	Dronabinol	95% of children received Dronabinol doses lower than guidelines, 55% of children received dronabinol as a scheduled medication, 19% of children received it 1 to 3 hours before chemotherapy, no data reported on benefits
Kennedy 2022	Retrospective observational study	Cystic Fibrosis	NA	64	Dronabinol	1 patient was taking dronabinol
Hoffenberg 2018	Chart review and survey	Inflammatory Bowel Disease	mean 16.2 (range 13-23) years	99	Medical cannabis	32/99 (32%) used medical cannabis use ever, 9/99 (9%) use it daily, no data reported on benefits
Rudich 2003	Case series	Chronic Neuropathic Pain	15, 14 years	2	Dronabinol	In patient 1, 45% reduction in pain intensity and patient 2 no change in pain intensity

Sun 2022	Retrospective cohort study	Chronic non-cancer pain	median 14.0 (IQ range 11.8–16) years	28	Nabilone	7/28 (25%) reported improvement in pain with Nabilone treatment
Polito 2018	Retrospective medical record review	Cancer	median 14 (range 1.2- 18) years	110	Nabilone	42/83(50.6%) and 14/26 (53.8%) of patients receiving highly and moderately emetogenic chemotherapy experienced acute control of chemotherapy induced vomiting
Devinsky 2022	Prospective observational study	Refractory epilepsy	mean 25.6 (range 12-46) years	29	CBD enriched Cannabis Herbal Extract (CBD: THC 20:1, 50:1)	median change in seizure from baseline to maximal dose period was-5.3% (IQR = -39% – 28.6%), ≥ 50% reduction in convulsive seizures 6/29 (21%), median changes in average seizure duration -2.5 (12.8) seconds
Sulak 2017	Retrospective observational study	Refractory epilepsy	range 2-46 years	272	CBD enriched Cannabis Herbal Extract with added THC and THCA	1–25% reduction in seizures 29/272, 26–50% reduction in seizures 60/272, 51–75% reduction in seizures 45/272, 76–99% reduction in seizures 75/272, complete clinical response 26/272
Hoffenberg 2019	Descriptive observational study	Inflammatory Bowel Disease	range 13-23 years	15	Cannabis Herbal Extract	15 users for medical cannabis, 9/15 used in past 30 days, major reason was to improve sleep quality, nausea, and increase appetite
Siani-Rose 2023	Prospective observational study	Autism Spectrum Disorder	range 6-12 years	18	Cannabis Herbal Extract	No data reported on benefits , 65 cannabis responsive biomarkers were identified, major ones are N-acetyl aspartic acid, spermine, deshydroasoandrosterone 3-sulphate
Kritikos 2022	Observational study	Cachexia, muscle spasm, pain, seizure, nausea, and cancer	NA	16727	Cannabis herbal extract, balanced CBD THC, low CBD high THC, high CBD low THC	No data reported on benefits
Doherty 2020	Retrospective medical record review	Cancer	mean 8.3 (3.6 months–19 years)	21	Cannabis herbal extract High CBD, High THC, balanced	21/21 improvement in nausea and vomiting, improvement in seizures 7/21 (64%), no improvement in seizure 2/21 (27%) and worsen seizure 1/21 (9%)
Achenbach 2020	Case series	Huntington's disease	mean age in pediatric cohort 10.3±4.1 years	16	Nabiximol in 1 patient	Nabiximol improved dystonia
Braun 2023	Retrospective medical record review	Refractory epilepsy	median 10 (range 0.25-35) years	30	CBD (Epidiolex®), artisanal marijuana, and hemp-based formulation	≥50% reduction in seizure frequency 12/30, < 50% reduction 18/30

Press 2015	Retrospective medical record review	Refractory epilepsy	mean 7.33 (range 0.5-18.25) years	75	CBD only, oral cannabis extract, Tetrahydrocannabinolic acid	Some improvement in seizure 43/75 (57%), > 50% reduction in seizures 25/75 (33%), complete seizure freedom 2/75% (0.3%)
Dale 2021	Observational study	CDKL5 Deficiency Disorder	Cannabinoid group1.5 (IQR 0.8–2.0) years, non-cannabinoid group 1.5 (IQR 1.0–2.3) years	82	CBD	Temporary improvement in seizures 11/82 (16%), no effect 16/82 (24%), and improvement in seizure 54/82 (38%)
Zürcher 2022	Retrospective medical record review	Spasticity, pain, lack of weight gain, vomiting, or nausea, epilepsy, ADHD, cancer, tics, inflammatory conditions,	median 11.5 (IQR 6-16) years	90	THC, CBD, and both	59/90 (66%) patient reported treatment success, 28/90 (31%) no benefit, 3/90 (3%) missing data
Zafar 2020	Retrospective observational study	Refractory epilepsy	range 2-48 years	10	CBD (9%) and THC (<1%) product, THC (14%), CBD (<1%)	mean reduction in monthly seizure frequency 97%, reduction in antiepileptic drugs from a mean 8 ±5.98 to 1 ±1.05
Zafar 2021	Case series	Refractory epilepsy	mean 6.2 (range 1-13) years	10	Whole plant cannabis extract <1%THC and 9% CBD, 14% THC and <1%CBD, <1%THC and 20% CBD, <1%THC and 10.6% CBD, <1%THC and 10% CBD	86% reduction in seizure frequency in all 10 children
Singh 2013	Case report	Cancer	14 years	1	Cannabis Herbal Extract	CHE decreased the blast cell count in a dose dependent manner
Lorenz 2004	Case series	Neurodegenerative disease, mitochondriopath	3, 8.9, 12, 12, 11, 13, 14, 14 years	8	THC	THC treatment was discontinued due to side effects and lack of benefits in all the patients

		y, post-hypoxic state, epilepsy, posttraumatic reaction				
Wang 2020	Prospective observational study	Refractory epilepsy	median 11 (4.5) years	9	THC enriched Cannabis Herbal Extract	Peak concentration of THC 0.8 to 3.6 ng/ml was achieved in 2 hours, no data reported on benefits
Szejko 2019	Case report	Tourette syndrome	12 years	1	THC	THC treatment was reported to reduce Tics
Lacey 2022	Retrospective medical record review	Cancer	17-87 years	412	THC, CBD, and both	No data reported on benefits
Schubert-Bast 2019	Prospective observational study	Dravet syndrome	median 8.5 (4.5-14.2) years	93	CBD	No data reported on benefits
Anderson 2019	Retrospective medical record review	Cancer	median 59 years	1120	Medical cannabis (unspecified)	Patient reported 30 or greater improvement in anxiety (22.8%), lack of appetite (18.7%), depression (22.4%), disturbed sleep (20.1%), fatigue (10.5%), nausea (20.2%), pain (11.5%), vomiting (28%)
Leung 2022	Observational study	Cancer and chronic pain	range 14-50 years	22015	Medical cannabis (unspecified)	No data reported on benefits
MacPhail 2022	Observational study	Pain, anxiety, sleep disorders, cancer, neuropathy, PTSD, epilepsy, convulsions, ASD	range 0-103 years	< 18 years 2,978	CBD and THC products	No data reported on benefits
Kilcher 2017	Observational study	Chronic pain, spasticity, neuropathic pain, lack of appetite, nausea, tremor, and epilepsy	range 10-99 years	1193	Medical cannabis (unspecified)	No data reported on benefits
Ofir 2019	Retrospective medical record review	Cancer	range 7 months to 21 years	50	CBD, CBD, and THC, and THC	No data reported on benefits
Fennessy 2018	Case report	Refractory epilepsy	5 years	1	Cannabis extract	Cannabis extract was reported to be beneficial

Singh 2022	Case report	Refractory epilepsy	2 years	1	purified CBD	Purified CBD had detrimental effect on patient's health leading to increase in liver function test
Labigalini 1999	Observational study	Substance use disorder	range 16- 28 years	25	Cannabis (unspecified)	17 (68%) reported reduction in crack-related symptoms
Hoffenberg 2108	Observational study	Inflammatory Bowel Disease	range 13-22 years	99	Medical cannabis (unspecified)	16 children reported using cannabis to relieve pain
Kolena 2016	Observational study	Medical purposes (unspecified) and Cancer	mean 31.2 (range 12-67) years	717	Medical cannabis (unspecified)	No data reported on benefits
Hazekamp 2013	Observational study	Multiple indications including pain, cancer, nausea, glaucoma, and HIV related symptoms, and epilepsy	mean 55.6 (14-93) years	5540	CBD, THC, and CBD as well as THC products	No data reported on benefits
Skrypek 2019	Observational study	Cancer	median 15.3 (range 1.4- 28.7) years	101	Medical cannabis (unspecified)	No data reported on benefits
Vaillancourt 2020	Retrospective medical record review	Refractory epilepsy, anxiety, nausea, sleep, pain,	mean 8.1 ± 4.1 years	37	Cannabis, marijuana, cannabidiol/tetrahydrocannabinol, cannabidiol-tetrahydrocannabinol buccal, and cannabidiol-tetrahydrocannabinol 2.5–2.7 mg/actuation buccal spray	21/27 had reduction in seizure frequency
Harrison 2013	Case series	Non-cancerous pain	16, 17, and 17 years	3	Medical cannabis (unspecified)	Medical cannabis was not effective in pain in all the 3 cases
Weaver 2019	Case report	Refractory epilepsy and neuropathic pain	6 years	1	Medical cannabis (unspecified)	Medical cannabis was reported to reduce seizure frequency and duration

Surveys and qualitative interviews						
Hussain 2015	Cross-sectional survey	Infantile Spasms and Lennox–Gastaut syndrome	mean 5.5 (range 3.0–24.0) years	117	CBD-enriched Cannabis extract	Complete seizure freedom 16 (14%), an increase in seizure frequency 5 (4.2%), No change 11 (9.4%), reduction in seizure frequency 100 (85%), complete seizure freedom 16 (14%)
Harte 2022	Qualitative interview	Refractory epilepsy	Parents of children 2-18 years	19	CBD	CBD was reported to reduce seizure frequency and severity in one third of patients, key themes emerged were seizure activity, family and school engagement, drug safety and legal access, efficacy, clinical support, social acceptance of the medication and program delivery
Sourbron 2022	Cross-sectional survey	Epilepsy	Parents of children -18 years	515	Cannabis-derived products and other antiepileptic drugs	Several antiseizure medication were prescribed
Pesantez-Rios 2017	Cross-sectional survey	Refractory epilepsy	NA	15	CBD	50% reduction in seizure 60%, complete seizure control 27%, sleep improved 50%, improvements in eating habits 43%, mood improvement 43%
Klotz 2018	Cross-sectional survey	Refractory epilepsy	NA	155 pediatricians	CBD, THC, and CBD, THC in combination	No data reported on benefits
Klotz 2020	Cross-sectional survey	Refractory epilepsy	Parents/caregivers of children- mean age 11.1 ±7.4	378	CBD	77/106 reported CBD efficacious in reducing seizure frequency
Bonanni 2023	Qualitative interview	Dravet syndrome and Lennox-Gastaut syndrome	Pediatric and adult neurologist, NA	8	CBD	CBD treatment was reported to improve quality of life in seizure patients
Masataka 2022	Cross-sectional survey	Refractory epilepsy	mean 7.25 ±7.50 years	38	CBD	2/38 reported complete resolution of seizures, 15/38 reported decrease in seizure frequency
Ngampoopun 2022	Cross-sectional survey	Epilepsy	median 12 (range 3 months- 18) years	166	CBD	No data reported on benefits
El-Khouly 2021	Cross-sectional survey	Cancer	median 6.5 (range 1-16) years	120	CBD and/or THC	No data reported on benefits
Parry 2019	Cross-sectional survey	Epilepsy, palliative care, and fatigue	NA	28	CBD	No data reported on benefits

Sobo 2017	Qualitative interview	Refractory epilepsy	Parents of children with refractory epilepsy, NA	25	CBD and/or THC	No data reported on benefits
Ioannides 2022	Cross-sectional survey	Cancer	mean 62 (range 16-92) years	261	CBD oil, Cannabis herbal extracts, and medical cannabis (unspecified)	Patient reported CAM beneficial for pain, anxiety, quality of life, anticancer
Maertens 2022	Cross-sectional survey	Fragile X syndrome	median 20 (5-57) years	25	CBD	Parents and caregiver reported CBD to be beneficial and made a positive difference in children with fragile X syndrome
Porter 2013	Cross-sectional survey	Refractory epilepsy	range 2- 16 years	19	CBD	Positive effects: better mood 15/19, increased alertness 14/19, better sleep 13/19, decreased self-stimulation 6/19
Suraev 2018	Qualitative interview	Refractory epilepsy	mean 3.3 (range 0-14.2) years	41	Cannabis extract	75-100% reduction in seizure frequency 26/51, 50-75% reduction in seizure frequency, Adapted Patient Global Impression of Change very much improved 23/51, much improved 10/51
Schräder 2021	Cross-sectional survey	Epidermolysis Bullosa	median 19 (IQR 14-26) years	71	CBD and/or THC	Reduction in pruritus (median change in score -3), pain (median change in score -3) and disease severity, improvement in overall symptoms 46/48, overall pain 45/48, overall pruritis 40/44
DeGasperis 2020	Cross-sectional survey	Refractory epilepsy	median 10 (range 0–45) years	56	CBD and/or THC	No data on efficacy
Gilligan 2021	Cross-sectional survey	Epilepsy	Pediatric and adult neurologist, NA	62	CBD and/or THC	No improvement in seizures 1/62, mild improvement in seizures 2/62, significant improvement in seizures 1/62
Hazekamp 2013	Cross-sectional survey	Multiple indications	median 40.7 (range 14-76) years	953	CBD, THC, both CBD and THC, nabiximol, nabilone, dronabinol	No data reported on benefits
Morosoli 2021	Cross-sectional survey	Cerebral palsy	Physicians caring for children, NA	70	CBD, THC, both CBD and THC, nabiximol, dronabinol	32/70 reported strong treatment effect of medical cannabinoids, 10/70 reported weak and 1/70 reported insignificant effect
Garcia-Romeu 2022	Cross-sectional survey	Multiple indications (pain and nerve-related	mean 38 (range 1-86) years	808	CBD and/or THC	Reduced pain 28%, improved sleep 18%, seizure reduction 18%, improvement in anxiety 22%, mood 11% and improved quality of life 14%

		conditions, seizures, psychiatric, cancer, autism spectrum disorders, neurological and headache, sleep, autoimmune, poor QOL, gastrointestinal issues, movement disorders, and dermatological conditions)				
DiLiberto 2022	Cross-sectional survey	ASD	mean 9.9 (range 3.5- 19) years	89	THC, CBD, and both	No data reported on benefits
Clayton 2017	Cross-sectional survey	Cerebral palsy, developmental delays, brain injury and Angelmen Syndrome	mean 13.9 (range 7-40) years	15	Dronabinol	73.3% of parents reported dronabinol effective for treating agitation
Suraev 2017	Cross-sectional survey	Epilepsy	range 0-65 years	976	Medical cannabis (unspecified)	90% adults reported reduction in seizure frequency, 71% of parents reported success in reducing seizure
Todd 2017	Cross-sectional survey	Epilepsy	NA	983	Medical cannabis (unspecified)	86% reported positive effect of medical cannabis in managing seizures
Jacobs 2018	Cross-sectional survey	Multiple indications including refractory epilepsy, pain, anorexia, anxiety, psychosis, tournette syndrome	NA	88	Medical cannabis (unspecified)	No data reported on benefits

Issai 2020	Cross-sectional survey	Cancer	Pediatric oncologist, and caregiver of children, NA	69	Medical cannabis (unspecified)	Improvement in pain reported 10/13 caregivers
Oberoi 2022	Cross-sectional survey	Cancer	Pediatric oncologist and palliative care physician, NA	122	Medical cannabis (unspecified)	Cannabinoids were reported to be beneficial for the management of nausea and vomiting, chronic pain, poor appetite, and anxiety
Gunning 2022	Qualitative interview	Multiple indications including cancer	Clinicians, NA	18	Medical cannabis (unspecified)	No data reported on benefits
Wardell 2022	Cross-sectional survey	Multiple indications (Chronic pain, nausea/vomiting, lack of appetite, epilepsy, depression, anxiety, insomnia and other)	range 15-24 years	2735	Medical cannabis (unspecified)	No data reported on benefits
Gibbard 2021	Qualitative interview	Cancer and epilepsy	Parents of children with cancer and epilepsy, 22 months to 16 years	6 (epilepsy) and 4 (cancer)	Medical cannabis (unspecified)	Parent reported beneficial effect of cannabis in reducing seizures and managing nausea
Chapman 2021	Cross-sectional survey	Cancer	range 0- >18 years	64	Medical cannabis (unspecified)	14/14 patients using medical cannabis reported improvement in symptoms
Belanger 2018	Cross-sectional survey	Multiple indications including epilepsy	Pediatricians, NA	285	Medical cannabis (unspecified)	No data reported on benefits
Wadsworth 2022	Cross-sectional survey	Pain	range 16-65 years	44,119	Medical cannabis (unspecified)	79% and 78% respondents in Canada, 80% and 83% in US illegal states and 83% and 84% in USA legal states responded using cannabis for pain as an alternative to opioids or prescription pain medications
Müller-Vahl 1998	Cross-sectional survey	Tourette syndrome	mean 30.3 (range 15-64) years	64	Medical cannabis (unspecified)	14/17 (82%) reported a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges and obsessive-compulsive symptoms

Grotenhermen 2003	Cross-sectional survey	Multiple indications (multiple sclerosis, Tourette syndrome, HIV/AIDS, migraine/headache, hepatitis C, depression, sleep disorders, spinal cord injury, and back pain, asthma, allergy, fibromyalgia, menstrual pain, and epilepsy)	mean 40.3 (16-87) years	143	Medical cannabis, THC	74.8% of patients reported cannabis to be beneficial
Ofir 2014	Cross-sectional survey	Cancer	Nursing team caring for pediatric cancer, NA	NA	Medical cannabis (unspecified)	NA
Podda 2020	Cross-sectional survey	Cancer	15-24 years	66	Medical cannabis (unspecified)	Patient reported improvement in sleep, anxiety, pain, nausea, and appetite with cannabis
Rychert 2020	Cross-sectional survey	Multiple indications (pain, neurological conditions, sleep conditions, mental health, substance abuse, cancer symptoms and other conditions)	mean 39.3 (range 16-90) years	3634	Medical cannabis (unspecified)	No data reported on benefits
Pledger 2016	Cross-sectional survey	Multiple indications including cancer	mean 48.9 years (15-55) years	13,009	Medical cannabis (unspecified)	No data reported on benefits
Klingenberg 2020	Cross-sectional survey	Refractory epilepsy	Pediatricians, NA	86	Medical cannabis (unspecified)	No data reported on benefits

Green-Murphy 2017	Cross-sectional survey	Cancer	Cancer patients < 18 years	143	Medical cannabis (unspecified)	No data reported on benefits
Finnegan 2019	Cross-sectional survey	Epilepsy	NA	389 (neurologist), 500 (primary care physicians), 401 (pediatricians)	Medical cannabis (unspecified)	No data reported on benefits
Ananth 2016	Cross-sectional survey	Cancer	Pediatric oncology care providers, NA	313	Medical cannabis (unspecified)	No data reported on benefits
Stephen 2020	Cross-sectional survey	Cystic fibrosis	range 12->35 years	193	Medical cannabis (unspecified)	28/31 (90.3%) reported cannabis effective for management of their symptoms related to cystic fibrosis
Ananth 2021	Qualitative interview	Cancer	Median 14.5 (range 2-21) years	15 (parents), 15 adolescent and young adult (15)	Medical cannabis	No data reported on benefits
Muirhead 2021	Cross-sectional survey	Cystic Fibrosis	NA	282	Medical cannabis	No data reported on benefits
Schlienz 2020	Cross-sectional survey	Multiple indications (neurological, chronic pain, neuropsychiatric, autoimmune, cancer, insomnia and other)	mean 38 (range 1-86) years	cannabis users 808, non-cannabis users 468	Medical cannabis (unspecified)	In the Cannabis user group, there was improved quality of life [$t(1054)=4.19, p<0.001$], better sleep [children: $t(224)=2.90, p<0.01$; adults: [$t(758)=3.03, p<0.01$], reduced anxiety [$t(1151)=4.38, p<0.001$], reduced average pain severity [$t(1150)=2.34, p<0.05$], higher health satisfaction [$t(1045)=4.14, p<0.001$],and reduced depression[$t(1210)=5.77$, $p<0.001$] reported in comparison with Control group
Sexton 2016	Cross-sectional survey	Multiple indications (pain, anxiety, depression, headache, nausea,	mean 36.3 (range 15-80) years	1429	Medical cannabis (unspecified)	No data reported on benefits

		spasticity, arthritis, others, pain, anorexia, cancer, ulcerative colitis, tics, tremors, epilepsy, multiple sclerosis, and HIV)				
Sivori 2023	Cross-sectional survey	Autism Spectrum Disorder	range 5-10 years	568	Medical cannabis (unspecified)	No data reported on benefits
Zhu 2022	Cross-sectional survey	Refractory epilepsy	range 0- >16 years	200	Medical cannabis, CBD	No data reported on benefits
Flavin 2020	Cross-sectional survey	Pain, spasticity, agitation,	parents or children, NA	215	Medical cannabis	No data reported on benefits
Zylla 2018	Cross-sectional survey	Cancer and cancer symptoms	Physicians	153	Medical cannabis (unspecified)	No data reported on benefits
Leung 2022	Cross-sectional survey	Multiple indications (pain, sleep, appetite, headache, nausea, epilepsy, and cancer)	range 16-65 years	27,169	Medical cannabis (unspecified)	No data reported on benefits
Gedde 2013	Cross-sectional survey	Refractory epilepsy	Parents of children	11	Cannabis herbal extract CBD: THC >16:1	98-100% reduction in seizure weekly seizure frequency 8/11, 75% reduction in weekly seizure frequency 1/11, 20-45% reduction in weekly seizure frequency 2/11
Cordiano 2021	Cross-sectional survey	Refractory epilepsy	Physicians, mean age 16	5	10% CBD oil	Physicians reported slight improvement in symptoms and excellent adherence to therapy in children with Lennox-Gastaut Syndrome, Rett syndrome, and West Syndrome
Aguirre-Velázquez 2017	Cross-sectional survey	Refractory epilepsy	parents, range 9 months - 18 years	53	CBD	Decrease in seizure in 81.3% of children; moderate to significant decrease in seizure frequency 51%, free from seizures 16% of cases, 9/43 reported reduction in antiepileptic drugs
Wilson 2020	Cross-sectional survey	Pantothenate Kinase-Associated Neurodegeneration	Families of children, mean 11 years	18	CBD, THC and 1:1 CBD: THC	Improvement in dystonia (4), pain (3), sleep (4), anxiety (3), and behavior (2) with in children with cannabis

Ananth 2018	Cross-sectional survey	Cancer	Pediatric oncology care providers, NA	288	Medical cannabis	No data reported on benefits
Baron 2018	Cross-sectional survey	Multiple indications including epilepsy, cancer and other	range 9-85 years	2032	Medical cannabis, Cannabis extract CBD: THC1:1, 3:1	No data reported on benefits

eTable 2.1.4. Safety outcomes reported in the included studies.[a]

Variables	Interventional reports (n=84)	Observational reports (n=131)
Study withdrawals		
Yes	50 (59.5%)	10 (7.6%)
No	19 (22.6%)	74 (56.5%)
Not reported	14 (16.7%)	36 (27.5%)
Unclear	1 (1.2%)	2 (1.5%)
Withdrawal reasons (check-in all that apply)		
Participant withdrawal	25 (29.8%)	3 (2.3%)
Investigator withdrawal	10 (11.9%)	0
Adverse event withdrawal	37 (44%)	7 (5.3%)
Lost to follow up	9 (10.7%)	1 (0.8%)
Protocol deviation	13 (15.5%)	0
Not reported	1 (1.2%)	1 (0.8%)
Studies reporting deaths	18 (21.4%)	12 (9.2%)
Deaths reported in intervention arms	69	45
Deaths reported in control arms	5	0
Common adverse events		
Somnolence	40 (47.6%)	18 (13.7%)
Diarrhea	39 (46.4%)	14 (10.7%)
Decrease in appetite	33 (39.3%)	10 (7.6%)
Vomiting	29 (34.5%)	14 (10.7%)
Pyrexia	17 (20.2%)	1 (0.8%)
Fatigue	14 (16.7%)	16 (12.2%)
Elevated transaminases	14 (16.7%)	10 (7.6%)
Dizziness	13 (15.5%)	7 (5.3%)
Nausea	12 (14.3%)	7 (5.3%)
Convulsion	12 (14.3%)	0
Pneumonia	12 (14.3%)	1 (0.8%)
Sedation	11 (13.1%)	10 (7.6%)
Irritability	11 (13.1%)	5 (3.8%)
Status epilepticus	10 (11.9%)	2 (1.5%)
Insomnia	9 (10.7%)	6 (4.6%)
Pruritus/Rash	8 (9.5%)	6 (4.6%)
Weight loss	8 (9.5%)	5 (3.8%)
Increased seizures	8 (9.5%)	13 (9.9%)
Infections	7 (8.3%)	2 (1.5%)
Upper respiratory infections	7 (8.3%)	1 (0.8%)
Agitation	6 (7.1%)	2 (1.5%)
Nasopharyngitis	6 (7.1%)	1 (0.8%)
Dry mouth	6 (7.1%)	1 (0.8%)
Anxiety	6 (7.1%)	4 (3.1%)
Ataxia	6 (7.1%)	2 (1.5%)
Increase in appetite	6 (7.1%)	7 (5.3%)
Constipation	4 (4.8%)	5 (3.8%)

Cough	4 (4.8%)	1 (0.8%)
Anorexia	4 (4.8%)	3 (2.3%)
Mood changes	4 (4.8%)	5 (3.8%)
Euphoria	4 (4.8%)	4 (3.1%)
Increase in weight	4 (4.8%)	4 (3.1%)
Tachycardia	3 (3.6%)	2 (1.5%)
Psychomotor hyperactivity	3 (3.6%)	2 (1.5%)
Fall	3 (3.6%)	2 (1.5%)
Headache	3 (3.6%)	4 (3.1%)
Lethargy	3 (3.6%)	4 (3.1%)
Behavior disorder	3 (3.6%)	8 (6.1%)
Depression	3 (3.6%)	2 (1.5%)
Seizures	3 (3.6%)	1 (0.8%)
Abdominal pain	3 (3.6%)	1 (0.8%)
Restlessness	3 (3.6%)	3 (2.3%)
Hypotension	3 (3.6%)	2 (1.5%)
Respiratory tract infection	2 (2.4%)	1 (0.8%)
Muscle twitch	2 (2.4%)	1 (0.8%)
Urinary retention	2 (2.4%)	3 (2.3%)
Eye redness	2 (2.4%)	1 (0.8%)
Confusion	2 (2.4%)	3 (2.3%)
Gastroenteritis	5 (5.9%)	1 (0.8%)
Sepsis	2 (2.4%)	1 (0.8%)
Blurry vision	2 (2.4%)	1 (0.8%)
Application site dryness	2 (2.4%)	1 (0.8%)
Hyperammonemia	2 (2.4%)	1 (0.8%)
Concentration difficulties	2 (2.4%)	1 (0.8%)
Hypernatremia	2 (2.4%)	1 (0.8%)
Anemia	2 (2.4%)	1 (0.8%)
Brain edema	2 (2.4%)	2 (1.5%)
Aggression	2 (2.4%)	3 (2.3%)
Bruise	2 (2.4%)	1 (0.8%)
Sleep disturbances	2 (2.4%)	12 (9.1%)
Influenza	2 (2.4%)	1 (0.8%)
Viral infection	2 (2.4%)	1 (0.8%)
Light-headedness	2 (2.4%)	2 (1.5%)
Cold	2 (2.4%)	1 (0.8%)
Loose teeth	2 (2.4%)	1 (0.8%)
Drowsiness	0	4 (3.1%)
Nocturia	1 (1.2%)	3 (2.3%)
Drooling	1 (1.2%)	3 (2.3%)
Hallucinations	1 (1.2%)	2 (1.5%)
Seizure exacerbation	0	2 (1.5%)
Dysphoria	0	2 (1.5%)
Movement disorder	0	2 (1.5%)
Tiredness	0	2 (1.5%)
Weakness	0	2 (1.5%)

Otitis media	2 (2.4%)	2 (1.5%)
Enuresis	0	2 (1.5%)
Urticaria	1 (1.2%)	2 (1.5%)
Others	1 (1.2%) each [#]	1 (0.8%) each[$]

#Pain in extremity, Syncope, Respiratory depression, Blisters, Mood issues, Blood and lymphatic system disorder, Poor sleep, Fever, Eosinophil count abnormal, Flatulence, Twitchiness, Forward lean, Nightmare, Gagging, Pharyngitis, Difficulty sleeping, Contact dermatitis, Disorientation, Scratch, GI discomfort, Decreased concentration, Thrombocytopenia, Body tilt, Heavy eyed, Neck pain, Heightened awareness, Hazy vision, Hepatotoxicity, Paranoia, Hot flushes, Polyuria, Hydrocephalus, Pressure sore, Abrasion, Reduced motility, Hyperhidrosis, Endocrine disorders, Enuresis, Hypertension, Epistaxis, Hypoalbuminemia, Decreased coordination, Hypokalemia, Temor, Worsening seizures, Drug concentration increased, Allergic reaction, Breath-holding, Excitations, Increased alanine aminotransaminase, Wheeze, Increased concentrations, Nervousness, Increased intracranial pressure, Increased non-epileptic clonus, Increased postictal period, Paranesthesia oral, bad dreams, Persistent tremor, Increased self-stimulation, Balance disorder, Increased slapping head on bed, Poor concentration, increased thirst, Precocious puberty, Cardiac disorders, Altered sleeping pattern, Emotional lability, Catatonia, Reduced water intake, Intracranial hypertension, Respiratory distress syndrome, Catheter site pruritus, Acute respiratory distress syndrome, Jitteriness, Darkening of port-wine birthmark, Laceration, Sensory hypersensitivity, CNS disorders, Skin mark, Slurred speech, Limb injury, Spasticity, Asthenia, Stereotypy, Low cardiac output state, Deep venous thrombosis, Low mood, Temporary amnesia, Memory loss, Tics, Metabolic acidosis, Tonsillitis, Eating disorders, Dehydration, Mouth sores, Urinary tract infection, Mouth ulceration, Vagueness, Difficulties in language retrieval, Ecchymosis, Diabetes insipidus, Colic, Facial twitch, Eczema, and Incontinence.

$ Nose bleeds, Retching/reflux, Abnormal movements, Low mood, Decreased concentration, Precocious puberty, Decreased coordination, Stereotypy, Deep venous thrombosis, Lack of coordination, Dehydration, Bad dreams, Paranoia, Balance disorder, Reduced water, Diabetes insipidus, Shaking, Diabetes-related hyperglycemia, Tics, Abrasion, Intracranial hypertension, Difficulties in language retrieval Loose stools, Mouth sores, Disinhibition, Nervousness, Disorientation, Acid reflux, Abnormal gait, Psychoactive effect, Drop attacks, Respiratory distress, Blisters, Drug concentration increased, Slurred speech, Cortical atrophy, Blood and lymphatic system disorder, Transient hemiparesis, Vagueness, Eating disorders, Jitteriness, Ecchymosis, CNS disorders, Eczema, Loss head control, Acute respiratory distress syndrome, Metabolic acidosis, Emotional lability, Neck pain, Endocrine disorders, Nightmare, Opisthotonos, Pancreatitis, Eosinophil count abnormal, Pharyngitis, Epistaxis, blurry vision, Concentration difficulties, Excitations, Regression in development, Facial twitch, , Scratch, Body tilt, Sensory hypersensitivity, Skin mark, Flatulence, Spasticity, Forward lean, Swollen eyelids, Gagging, Temporary amnesia, Gait abnormality, Tonsillitis, Twitchiness, GI discomfort, Urinary tract infection, gums/nose bleeding, vocal yelling, Gurgling sounds followed by suddenly dropping limp to ground, Chest pain, Bradycardia, Laceration, Hand cramp, Cholecystitis, Limb injury, Heavy eyed, Heightened awareness, Low cardiac output state, Hepatobiliary disorders and asthenia, Memory loss, Hepatotoxicity, Cognitive slowing, Hiccups, Mouth ulceration, Hot flushes, Hydrocephalus, Allergic reaction, Hyperemia, Negative side effects, New-onset non-epileptic seizures (NES), Hyperhidrosis, Colic, Not able to walk, Hypertension, Hazy vision, Hyperthermia, Pain in extremity, hypoalbuminemia, Paraesthesia oral, Hypokalemia, Persistent tremor, Breath-holding, Photosensitivity, Hypotonia, Polyuria, impaired ability to think, Improved concentration, pressure sore, Improved language skills, Psychiatric changes, Improved motor skills, Concentration difficulties, Improved night sleep, educed motility, Improved sleep quality, Reduced water intake, Inability to eat, Respiratory depression, Incontinence, Respiratory distress syndrome, Increased energy, Asthenia, Rhabdomyolysis, Increase in plasma concentration of Clobazam, Cardiac disorders, Catatonia, Sialorrhea, Worsening behavior, Worsening seizures, Contact dermatitis, Apathy, Conclusion, Increased ketones, Stomach pain eosinophilia, Increased lipase, syncope, Increased non-epileptic clonus, Temor, Increased postictal period, Thrombocytopenia, Increased rescue medications, Catheter site pruritus, Transient diarrhea at treatment onset, Increased self-stimulation, Tremor, Increased slapping head on bed, Unexplained laugh, Increased thirst, Crying, Increased tone, Change in tone patterns, Darkening of port-wine birthmark, Changed bowel moment, Wheeze, Increased alertness, Worsening EEG, Increased comprehension, Xerophthalmia, and Increased intracranial pressure.

a in this table, 'n' refers to the number of studies reporting the specified safety outcome, not the number of individual patients experiencing the event.

2.1.13.2 List of the included studies

2.1.13.2.1 Included interventional studies

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2.1.13.3 Search strategy

2.1.13.3.1 Multifile Ovid Search

Embase <1974 to 2021 June 16>
Ovid MEDLINE(R) ALL <1946 to June 16, 2021>
APA PsycInfo <1806 to June Week 1 2021>

1 Cannabis/

2 exp Cannabinoids/

3 Cannabaceae/

4 Medical Marijuana/

5 Marijuana Use/

6 Marijuana Smoking/

7 cannab*.tw, kf.

8 Mari?uana*.tw, kf.

9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw, kf.

10 (19GBJ60SN5 or 2N4O9L084N or 7J8897W37S or K4H93P747O).rn.

11 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw, kf.

12 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw, kf.

13 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw, kf.

14 or/1-13 [CANNABIS CONCEPT]

15 exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. [CHILDREN CONCEPT]

16 14 and 15

17 exp Animals/ not (exp Animals/ and Humans/)

18 16 not 17 [EXCLUDING ANIMAL ONLY STUDIES]

19 (202106* or 202107* or 202108* or 202109* or 20211* or 2022*). dt, ez, da.

20 18 and 19

21 20 use medall

22 cannabis/

23 exp cannabinoid/

24 cannabaceae/

25 exp "cannabis (genus)"/

26 medical cannabis/

27 exp "cannabis use"/

28 cannab*.tw, kw.

29 Mari?uana*.tw, kw.

30 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw, kw.

31 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw, kw.

32 (8063-14-7 or 1972-08-3 or 13956-29-1 or 51022-71-0 or 8001-54-5 or 33086-25-8 or 36557-05-8 or 24359-49-7).rn.

33 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw, kw.

34 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw, kw.

35 or/22-34

36 exp child/ or exp newborn disease/ or exp infant/ or exp adolescent/ or exp pediatrics/ or abandoned child/ or gifted child/ or orphaned child/ or unwanted child/ or "minor (person)"/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

37 35 and 36

38 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

39 Animal experiment/ not (human experiment/ or human/)

40 38 or 39

41 37 not 40

42 limit 41 to dc=20210617-20220427

43 42 use oemezd

44 exp cannabis/

45 exp cannabinoids/

46 marijuanas/

47 marijuana usage/

48 marijuana legalization/

49 cannab*.tw.

50 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw.

51 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw.

52 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw.

53 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw.

54 or/44-53 [Cannabis Concept]

55 limit 54 to (childhood <birth to 12 years> or adolescence <13 to 17 years>)

56 exp pediatrics/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

57 54 and 56

58 55 or 57

59 exp Animals/ not (exp Animals/ and Humans/)

60 58 not 59

61 60 use psyc17

62 60 use psyc18

63 60 use psyc16

64 or/61-63

65 21 or 43 or 64

66 remove duplicates from 66

**Note Ovid multifile search of MEDLINE, Embase, and PsycInfo were run on June 20 2020, June 17 2021, April 27 2022, and April 24 2023. The search remains unchanged except for date limits.*

2.1.13.3.2 Cochrane Library (Wiley) Search Strategy

ID Search

#1 MeSH descriptor: [Cannabis] this term only

#2 MeSH descriptor: [Cannabinoids] explode all trees

#3 MeSH descriptor: [Cannabaceae] this term only

#4 MeSH descriptor: [Medical Marijuana] this term only

#5 MeSH descriptor: [Marijuana Use] explode all trees

#6 MeSH descriptor: [Marijuana Smoking] this term only

#7 cannab*: ti, ab, kw

#8 Mari? uana*: ti, ab, kw

#9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla): ti, ab, kw

#10 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex): ti, ab, kw

#11 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726"): ti, ab, kw

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 MeSH descriptor: [Child] explode all trees

#14 MeSH descriptor: [Congenital, Hereditary, and Neonatal Diseases and Abnormalities] explode all trees

#15 MeSH descriptor: [Infant] explode all trees

#16 MeSH descriptor: [Adolescent] this term only

#17 MeSH descriptor: [Pediatrics] explode all trees

#18 MeSH descriptor: [Child, Abandoned] this term only

#19 MeSH descriptor: [Child, Exceptional] this term only

#20 MeSH descriptor: [Child, Orphaned] this term only

#21 MeSH descriptor: [Child, Unwanted] this term only

#22 MeSH descriptor: [Minors] this term only

#23 (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or "premature birth*" or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or "elementary school*" or "nursery school*" or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*):ti, ab, kw

#24 (child* or adolesc* or pediat* or paediat*):so

#25 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

**Note Cochrane Library search via Wiley were run on June 20, 2020, June 17, 2021, April 27, 2022, and April 24, 2023. The search remained unchanged except for date limits and a correction in a typo between June 2020 and June 2021 in Line #11 where ti, ab, kw was used instead of ti, ab, kw*

Section 2.2 Cannabinoids for symptom management in children with cancer: a systematic review and meta-analysis

2.2.1 Overview

In 2021, while data extraction for a Living Systematic Review (Chapter 2), we noticed a mounting number of studies investigating cannabinoid use for symptom management in children with cancer. We felt a need for critical appraisal of emerging literature on cannabinoid use in children with cancer to inform clinical practice and prospective research.

In this systematic review, we evaluated the available evidence on cannabis products used for symptom management in children with cancer with regard to their safety, dosing, and efficacy. The evidence from this systematic review will inform future clinical trials on cannabinoids use for symptom management in children with cancer.

Cannabinoids for symptom management in children with cancer: a systematic review and meta-analysis

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2.2.2 Abstract

Background: Despite the widespread use of medical cannabis, little is known regarding the safety, efficacy, and dosing of cannabis products in children with cancer. Our objective was to systematically appraise the existing published literature for use of cannabis products in children with cancer.

Methods: This systematic review (PROSPERO ID: CRD42020187433) searched four databases: MEDLINE, Embase, PsychInfo, and Cochrane Library. Abstracts and full text were screened in duplicate. Data on types of cannabis products, doses, formulations, frequency, routes of administration, indication, clinical and demographic details, and reported efficacy outcomes were extracted. Data on cannabinoid-related adverse events were also summarized.

Results: Of 34,611 identified citations, 19 unique studies with a total of 1,927 participants with cancer were included: 8 retrospective chart reviews, 7 randomized controlled trials, 2 open-label studies, and 2 case reports. Included studies reported the use of various cannabis products for symptom management. Cannabinoids were commonly used for management of chemotherapy-induced nausea and vomiting (11/19, 58%). In controlled studies, somnolence, dizziness, dry mouth, and withdrawal due to adverse events were more common associated with the use of cannabinoids. Across all included studies, no serious cannabis-related adverse events were reported.

Conclusion: While there is evidence to support the use of cannabis for symptom management, in children with cancer, there is a lack of rigorous evidence to inform dosing, safety, and efficacy of cannabinoids. Given the increasing interest in using cannabis, there is urgent need for more research on medical cannabis in children with cancer.

Keywords: Medical cannabis; children; cannabidiol; tetrahydrocannabinol; cancer symptoms; chemotherapy induced nausea and vomiting

2.2.3 Introduction

Advanced diagnostic, surgical, and radiation techniques, alongside effective chemotherapeutic regimens, have improved survival rates among children diagnosed with cancer.(1) This improved survival comes at the cost of many treatment-related side effects such as nausea, vomiting, pain, and anorexia.(2) Also, as a cure is not possible for every child with cancer, many children still suffer from the symptoms related to advanced cancer such as pain, anorexia, anxiety, and weight loss. Multiple studies have shown the association of uncontrolled cancer or cancer treatment-related symptoms with inferior quality of life.(3) Hence, in the last two decades, greater effort has been directed towards providing enhanced supportive care to these children.(4) However, despite advancements in supportive care, many children with advanced cancer continue to report uncontrolled cancer or treatment-related symptoms, and reduced quality of life.(5, 6)

Over the last decade, cannabis products - both synthetic cannabinoids and natural phytocannabinoids - have gained popularity for symptom management among children for various conditions including cancer, chronic headaches, refractory epilepsies, and neuropathic pain.(7-10) Cannabidiol (CBD) and tetrahydrocannabinol (THC) are the most abundant phytocannabinoids produced by the plant cannabis and are of therapeutic interest in children with cancer.(10) Cannabinoids bind to cannabinoid 1 (CB1) receptors and prevent the release of emetogenic neurotransmitters.(11) Randomized controlled trials (RCTs) conducted in adult patients report benefits of cannabinoids in preventing chemotherapy induced nausea vomiting (CINV) and reducing cancer related pain.(12, 13) Synthetic cannabinoids are also effective in managing acute CINV.(14, 15) Nabilone and dronabinol, both synthetic cannabinoids, are approved for the treatment of the CINV in Canada (nabilone) and the United States (dronabinol

and nabilone).(16) Several recently published reports have also shown that cannabinoids are beneficial for the management of cancer-related pain by inhibiting thalamic or spinal nociceptive neurons and c fiber conduction.(17-19)

Historically, strict laws regulating cannabis have precluded undertaking studies of children in cannabis clinical trials, limiting the understanding of the efficacy of cannabis in children.(20) Despite this, due to the reports of improvements in symptoms including pain, nausea, vomiting, sleep, mood, and appetite with cannabis, some parents have elected to access cannabis products for their child with cancer off label.(21, 22)

Pediatric oncologists are understandably reluctant to authorize cannabis due to a lack of evidence supporting the safety and efficacy of use in children with cancer.(6) There is a strong need to map the evidence on the current use of cannabinoids in children with cancer to inform the development of clinical trials evaluating the safety, dosing, and efficacy of various cannabis products in children with cancer. Therefore, we sought to systematically review the literature on the use of medical cannabinoids for symptom management in children with cancer. The primary objective of this review was to evaluate the available evidence *on cannabis products used for symptom management in children with cancer with regards to their safety, dosing, and efficacy*.

2.2.4 Materials and methods

2.2.4.1 Protocol registration and reporting

The review protocol was registered with PROSPERO (registration number CRD42020187433). We followed PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) and PRISMA-S guidelines and the Cochrane Collaboration reporting items for reporting this systematic review.(23-25)

2.2.4.2 Eligibility criteria

We included all studies that met the following criteria: enrolled at least one child aged ≤ 18 years with cancer receiving any forms of natural or pharmaceutical-grade cannabis administered for symptom management, with or without comparator. We excluded studies related to accidental, recreational exposure of cannabis and studies conducted in adult patients only.

2.2.4.3 Search strategy

An experienced health sciences librarian (ML) designed the search strategy in MEDLINE (Ovid) using a combination of subject terms and keywords; it was peer-reviewed by another health sciences librarian using the Peer-Review of Electronic Search Strategies (PRESS) checklist.(26) The search concepts included terminology related to cannabis (hemp, marijuana, cannabidiol, etc.) and children or adolescents (preschool, teenagers, etc.). The search was then translated using appropriate terminology for each other database. The following databases were searched from inception to June 20, 2020 (with updates run on June 17, 2021, and April 27, 2022): MEDLINE (Ovid), Embase (Ovid), PsycInfo (Ovid), and the Cochrane Library (Wiley). There were no study type or date limits applied but searches were restricted to human studies available in English or French. The MEDLINE, Embase, and PsycInfo searches were run simultaneously in Ovid and the Ovid deduplication tool was used. A grey literature search was also conducted. All database and trial registry results were deduplicated in Endnote 20 and uploaded to Covidence for screening. All database search strategies are available in **Appendix**.

2.2.4.4 Study selection, data extraction and quality assessment

Three independent reviewers (MC, AP, MB) performed first-pass screening (title and abstracts), second-pass screening (full-texts screening), data extraction and quality assessment, independently. Disagreements between the reviewers were resolved by Lauren Kelly (LEK). This

literature screening was part of a Living Systematic Review, where we included all types of studies related to medical cannabis in children without restricting to any medical condition. For this review, we have included studies where medical cannabis was used in children with cancer. Following variables were extracted from each study: author, year, country, study design, study population, sample size, inclusion criteria, duration of the study, age, sex, type of cancer, indications of cannabinoids used in children with cancer, cannabis dose, cannabis formulation, frequency route, cannabis-related adverse events, and primary outcome of the study. We detailed study characteristics in **Table 2.2.2**. We performed the quality assessment of retrospective treatment chart reviews, open-label (unblinded) and RCTs using the NIH quality assessment tool for case series, Joanna Briggs Institute (JBI) critical appraisal checklist for quasi-experimental studies and Cochrane Risk of Bias 1 (ROB 1) tool, as appropriate for study design.(27, 28)

2.2.4.5 Data synthesis and analysis

The narrative synthesis of extracted data was performed in Microsoft excel and we followed Synthesis without meta-analysis (SWiM) in systematic review guidelines.(29) Adverse event data was pooled with the help of review manager software (RevMan, version 5.3 for windows, the Cochrane collaboration, Oxford, UK). The random effect model was used to pool adverse event data using the Mantel-Haenszel method.

2.2.5 Results

2.2.5.1 Characteristics of included studies

Of 34,611 identified citations, we included 19 unique studies: 10 observational studies enrolling 1,529 children and 9 interventional studies with 398 participants. The study selection process is described in the PRISMA flow diagram in **Figure 2.2.1.** The characteristics of included studies varied broadly (described in **Table 2.2.1.**), 8 observational studies were

retrospective medical record reviews(8, 15, 30-35) and 2 were case reports,(36, 37) while 7 interventional studies were RCTs(38-44) and 2 were open-label (unblinded) studies.(45, 46) Adults were included along with children in 3 observational studies(33, 35, 47) and 5 interventional studies.(39, 42-45) The sample size of observational studies varied from 1 (case reports) to maximum of 1,120 participants (retrospective chart reviews), whereas in interventional studies sample size varied from 8 to 113 participants. CINV was the most common indication for use of cannabinoids in included studies (11/19, 58%) followed by other cancer symptoms (8/19, 42%) including epilepsy related to central nervous system tumor.

2.2.5.2 Quality appraisal

We appraised internal validity of included studies using the NIH quality assessment tool for case series; 6 observational studies were of good quality, 2 were poor and 1 of fair quality. In the study by Dorris et al. results were not reported adequately for interpretation,(30) whereas in the report by Warren et al. cases were not consecutive, subjects were not comparable, there was inadequate length of follow up, and outcomes were also not clearly defined.(37) In RCTs, 4 studies were with high risk of bias due to lack of blinding in one study,(44) incomplete outcome data in three studies.(38, 39, 41) In the other three RCTs, there was unclear risk of bias.(40, 42, 43) **Figure 2.2.2.** illustrates the assessment of the quality of randomized controlled trials. Non-randomized controlled trials were of moderate quality, as both the studies were dose finding studies without any control group.(45, 46) The complete quality assessment of the included studies is described in supplementary material (**eTable 2.2.2., eTable 2.2.3., eFigure 2.2.1.**).

2.2.5.3 Characteristics of study participants and cannabinoids used in the studies

The median age of participants in observational studies ranged between 6 months-18 years, while in interventional studies ranged between 3.6 months-18 years. **Table 2.2.2.** and

Table 2.2.3. describes the characteristics of the included study participants and cannabinoids used. A wide variety of cannabinoids were used for the management of CINV in children with cancer; nabilone (5/19, 26%), unspecified cannabis herbal extracts (5/19, 26%), delta-9 tetrahydrocannabinol (3/19, 16%), dronabinol (2/19, 11%), delta-8 tetrahydrocannabinol (1/19, 5%), levonantradol (1/19, 5%), unspecified cannabinoids (1/19,5%), and cannabidiol (1/19, 5%).

Type of cannabinoid was not specified by three observational studies.(8, 35, 47) Nabilone, (38, 41-43) and delta-9 THC,(39, 40, 44) were used primarily as interventions for the management of CINV; however, delta-8 THC (46) and levonantradol (45)(synthetic derivative of THC) were used for CINV prophylaxis. The most common dose of delta-9 THC in the trials was reported as 10 mg/m2, further it was administered in the form of capsules or inhaled.(40, 44) Nabilone dose varied in the trials from 0.5 mg to 2 mg. In most trials, delta-9 THC and Nabilone were administered 2 hours prior to the chemotherapy followed by every 4-6 hours. Cannabinoids were administered by oral route using capsules as formulation except levonantradol, which was administered intramuscularly in an open label dose finding study.(45) Most patient populations included in the chart review studies (7/8, 90%) had a diagnosis of brain tumor or leukemia/lymphoma. Types of cancer were not specified in the majority of included interventional studies.(39-43, 45) CINV (7/9, 80%) was the major indication for taking cannabinoids followed by pain and supportive care in cancer (6/9, 70%) among the included observational studies. For example, cannabinoids were used to manage epilepsy-related to brain tumors in 2 observational studies.(34, 37)

2.2.5.4 Efficacy of cannabinoids

Only interventional studies (n= 7) reported efficacy outcomes, overall, cannabinoids were reported to be superior in controlling nausea and vomiting compared to active control groups. We

did not pool the efficacy data due to lack of homogeneity among included trials. A randomized double blind crossover trial (nabilone vs domperidone) reported children in the nabilone arm experienced fewer episodes of nausea and vomiting.(38) Further, they also reported two-third of study participants preferred nabilone over domperidone.(38) A study conducted in the USA (nabilone vs prochlorperazine) also reported superiority of nabilone for relief of nausea and vomiting in patients receiving chemotherapy.(41) Additionally, they also reported 76% of their study participants continued taking nabilone as an antiemetic of choice after the completion of study. (41) Furthermore, a study conducted in the USA (nabilone vs prochlorperazine) observed similar efficacy of nabilone, they reported nabilone (90/113, 80%) was superior to prochlorperazine (36/113, 32%) in controlling nausea and vomiting in patients receiving chemotherapy. (43) Similarly, a double-blind study Ekert et al found delta-9 THC was superior in controlling nausea and vomiting compared to Metoclopramide. However, they also reported that few patients suffered from nausea and vomiting.(40)

In an open label dose finding study, Cronin et al, reported that levonantradol (delta-9-THC) was efficacious (25/28, 89%) in achieving completed or partial control of nausea, irrespective of age group(45) In another open-label study single arm study reported delta-8 THC was effective in complete control of nausea in all children.(45, 46)

2.2.5.5 Safety of Cannabinoids

Cannabinoid-related adverse events (AEs) reported by included observational studies are described in **eTable 2.2.1.** Major cannabinoid-related AEs reported by observational studies (2/10, 20%) were drowsiness, followed by dizziness, headache, and euphoria (supplementary material). Cannabinoid-related AEs reported in the interventional studies (**Table 2.2.4.**) included somnolence, increase in appetite, development of a ‘high,’ dizziness, and dry mouth. Study

withdrawals due to adverse events were more common in participants receiving cannabinoids compared to the comparator group (risk ratio: (RR) 3.67; 95%CI 0.61-21.89, 2 studies). There were higher risks of somnolence (RR 4.03; CI 1.23-1.84, 2 trials), development of a 'high' (RR 9; CI 4.38-18.48, 3 trials), dizziness (RR 4.57; CI 1.23-24.26, 3 trials), dry mouth (RR 2.42, CI 1.85-3.16, 2 trials), and increase in appetite (RR 8; 1.03-61.84, 2 trials) in the cannabinoid compared to control group.

2.2.6 Discussion

Cannabinoids are increasingly being used for symptom management in children with cancer with or without authorization (or medical advice) from pediatricians or health care professionals.(48) In this systematic review, we provide a comprehensive review and analysis of currently available evidence to inform clinicians, policymakers, and guide future research directions to examine the safety and efficacy of cannabinoids in children with cancer. We included interventional and observational studies including children with cancer. The management of CINV was the most studied indication for cannabinoids in both observational and interventional studies, leaving a knowledge gap on the impact of medical cannabis and cannabinoids related to pain, mood, sleep, anxiety, and health-related quality of life. Included studies in this review also use cannabis for the management of epilepsy in children with brain tumors.(8, 34) While cannabidiol has been shown to be effective for the management of drug-resistant epilepsies(49), there is a strong need to generate evidence on the safety and efficacy of CBD for seizure management in children with cancer, particularly in regard to how cannabinoids may act with other medications. RCTs evaluating responses to pain, mood, sleep, and health-related quality of life are also urgently needed to evaluate different combinations of cannabinoids, dosing schedules and safety outcomes.

The majority of included observational studies did not adequately describe the type of cannabinoids, dosing, frequency, and route of administration of cannabis products which hinders reproducibility and meta-analysis. Outcomes of observational studies were heterogeneous, there was no uniformity in reporting outcomes. On the other hand, there was a lot of heterogeneity in products currently being used in children with cancer. However, most of our included trials were from the late 1990s, and there was large variation in the reporting of efficacy outcomes. We were not able to pool the efficacy outcomes due to these variations. There is a strong need for interventional studies comparing safety and efficacy cannabinoids in children with cancer with available treatment options. There is also a need for cannabinoid researchers to work together on standards for reporting cannabis exposures and cannabis-related adverse events to ensure future research is optimally useful. Evidence is urgently required on the safety of cannabinoids with regards to different cannabis products, tolerability, and dose of cannabinoids in the vulnerable pediatric population diagnosed with cancer. Pediatric oncologists' express concerns around unknown cannabinoid dosing and product selection(6), which was highlighted in our findings by the lack of detailed cannabis exposure reported, particularly observational study designs. Considering lack of cannabis core set of outcomes tools, there is a scope of developing core set of outcomes for cannabinoid clinical trials in pediatric oncology. Additionally, there is scope for pediatricians to collaborate internationally to generate long-term safety and efficacy data of cannabinoids in children with cancer.

Most of the children receiving medical cannabis in included studies were diagnosed with CNS tumors and blood-related cancers.(8, 31, 34, 35) A recent systematic review on the safety and efficacy of medical cannabinoids in the child and adult population with seizures reported safety concerns with adverse mental events and a decrease in appetite. However, the safety data

of cannabinoids is limited to CBD use in epilepsy where randomized controlled trials have been conducted.(50)

Cannabinoids may be beneficial in management of pain, nausea and vomiting in children with cancer, especially where there is failure to respond to available therapeutics.(22, 51) In this systematic review, we pooled safety evidence from interventional studies and identified higher study withdrawal due to cannabinoids-related AEs than in the control groups. Cannabinoids possess a risk of developing adverse events such somnolence, increase in appetite, altered mood and perception, and dizziness.(52) Pawliuk et al., reported the safety of medical cannabis in scoping review and reported CBD is associated with long-term adverse events such as an increase in seizure frequency, weight gain/loss, fatigue, anorexia, diarrhea, and somnolence.(53) Our findings were consistent with their findings, but our data for safety was limited.(35)

There are certain limitations of this systematic review. Firstly, few studies were included in the review and methodological limitations of reporting resulted in limited recommendations for practice. Secondly, we included retrospective medical record reviews, and primarily non-randomized studies. As the overall quality of evidence was low, there was no uniformity of the outcomes in the included studies. However, the included clinical trials were published in late 19s, and interpretation of the study's findings were made considering this factor. Further, due to high variability in reporting of outcomes data we were not able to do quantitative synthesis of outcomes data. There were no case-control studies and cohort studies. Cannabinoids have a strong potential to interact with other drugs metabolized by the same pathway and increase the risk of adverse events.(54) There was very little reporting on what other medications study participants were taking at the time they were receiving cannabinoids, limiting our ability to provide guidance on drug-drug interaction safety precautions.

2.2.6.1 Future research directions

There is widespread, unregulated use of cannabinoids for symptom management in children with cancer.(35) This is in the context of a lack of safety and efficacy evidence. There is a strong need to fill the evidence gap and conduct studies investigating safety and tolerability of medical cannabis for symptom management in children with cancer. Collaboration across jurisdictions will be needed to efficiently study rare populations such as children with cancer. Innovative and multijurisdictional clinical trials, and rigorous observational studies with clear cannabis exposure definitions should be planned to evaluate long-term safety and efficacy to improve the quality of life of children with cancer and their families.(55)

2.2.7 Conclusion

Cannabinoids have been used for management of multiple symptoms in children with cancer, including CINV, anorexia, tumor-related epilepsy, and cancer-related pain. Cannabis products may have therapeutic applications for symptom management in children with cancer. However, there is a knowledge gap regarding their product composition, dose, short and long-term adverse events, and drug interactions. There is an urgent need to explore real word benefits and harms of cannabis in this vulnerable pediatric population. Our systematic review highlights the urgent need to generate high-quality evidence on the safety, dosing and efficacy of cannabis products used for symptom management in children with cancer.

2.2.8 Acknowledgement

We would like to acknowledge OA for her help with initial screening of LSR.

2.2.9 Author contribution statement

MC: conceptualization, data curation, formal analysis, investigation, project administration, software, visualization, study selection, writing - original draft, and writing ,

LEK: study selection, funding acquisition, supervision, project administration validation, methodology, resources, review, and editing; MB: review and editing, study selection, project administration; SRR: review and editing; AB: review and editing; AP: study selection, project administration; SO: review and editing, validation; NB: review and editing; Anthony Herbert: review and editing; ML: literature searches, review and editing

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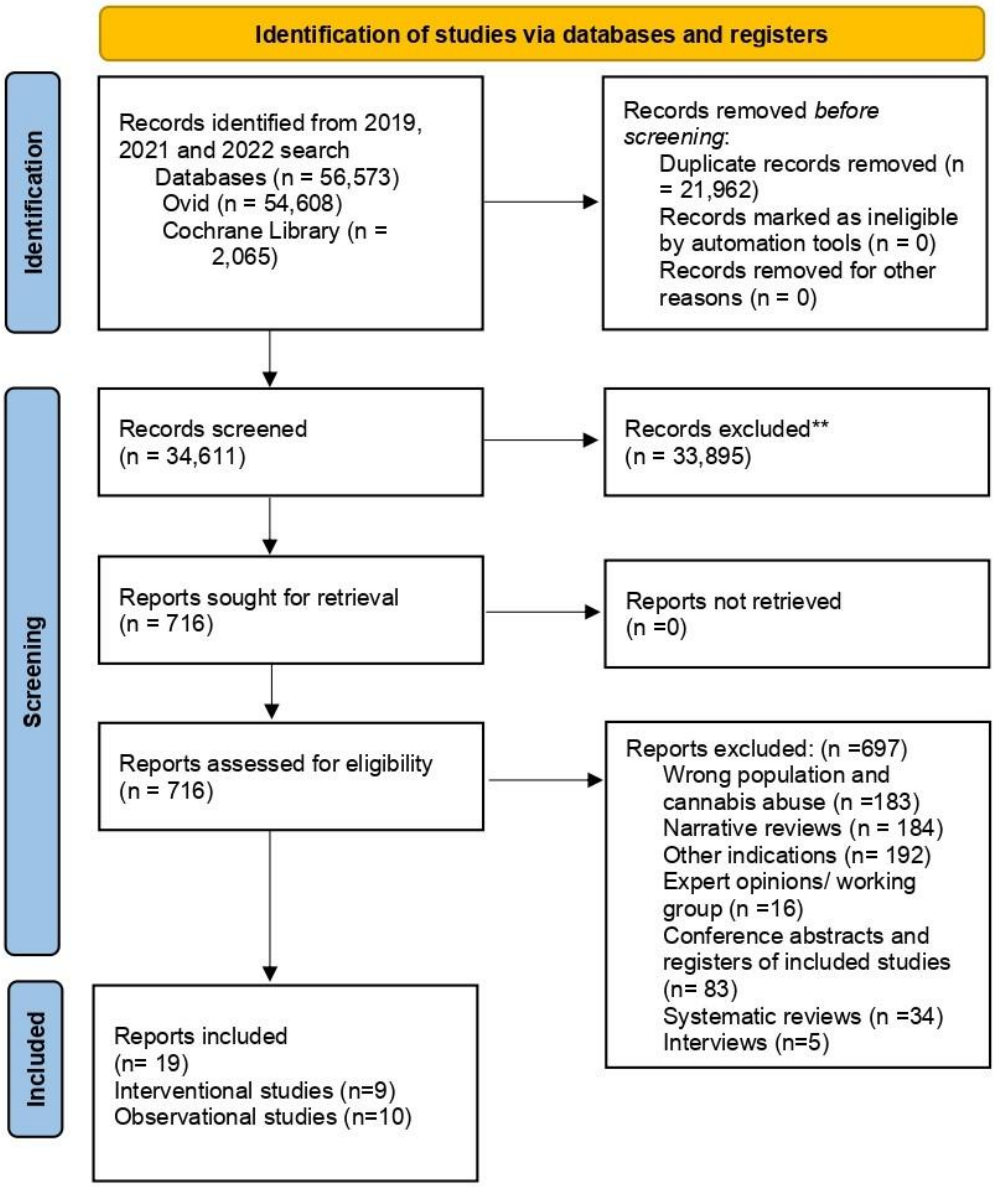
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2.2.11 Figures



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Figure 2.2.1. The PRISMA flow diagram of studies included in the systematic review.

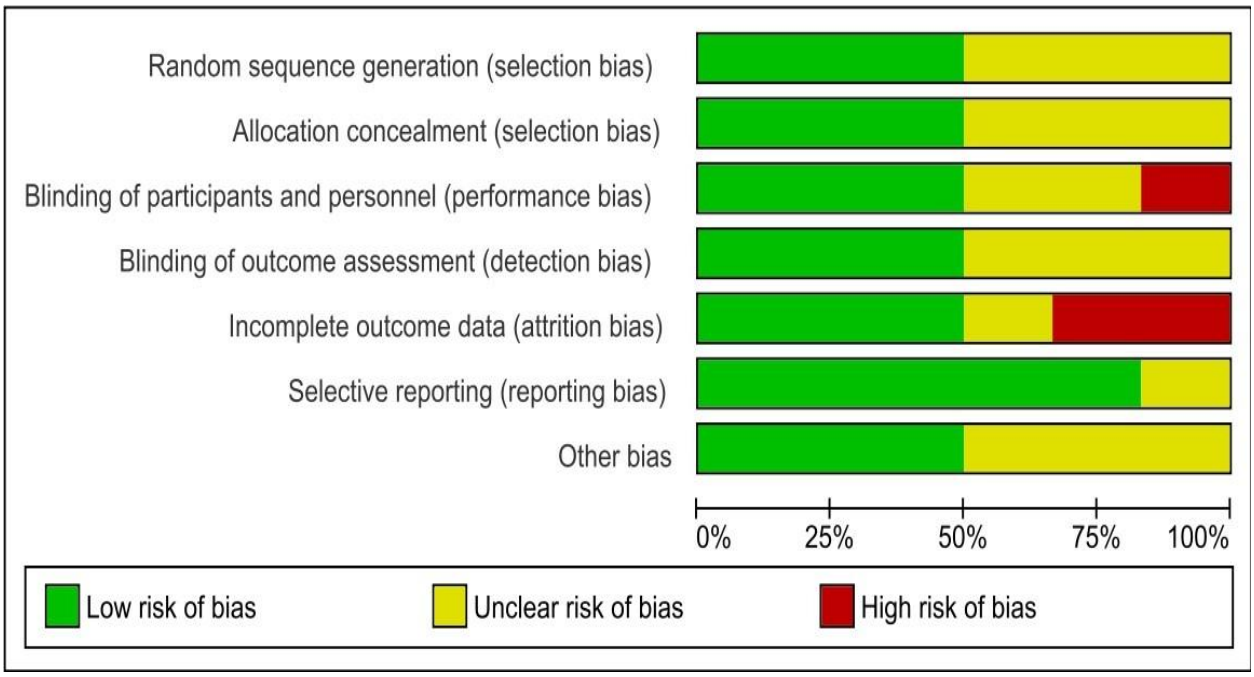


Figure 2.2.2. Risk of bias summary of the included randomized controlled trials.

2.2.12 Tables

Table 2.2.1. Characteristics of the included studies.

Author	Country	Study Design	Population	Indication	Sample Size	Inclusion Criteria	Duration of study
Skrypek 2019 (8)	USA	Observational; Retrospective medical record review	Children	Cancer and treatment-related symptom management	101	Patients were included if they had a cancer diagnosis from the Children's Minnesota Cancer and Blood Disorders database	July 2015- February 2019, 3 years 7 months
Elder 2015 (31)	USA	Observational; Retrospective medical record review	Children	CINV	58	Patients eligible for inclusion were those with malignancy ≤18 years old, who received at least 1 dose of dronabinol for CINV during admission.	January 2000-July 30, 10 years 6 months
Anderson 2019 (47)	USA	Observational; Retrospective medical record review	Children and adults	Cancer symptom management	1120	Patients who were certified for cancer and enrolled in the Minnesota medical cannabis program from July 1, 2015 to December 31, 2017 were identified through the program registry (specific cancer diagnoses are not collected in the registry), For analytic purposes, patients who had at least a 4-month observation window since starting medical cannabis	July 2015-December 2017, 2 years 5 month
Dorris 2018 (30)	USA	Conference abstract, Prospective Observational study	Children	CNS tumor	26	Pediatric CNS tumor patients who self-medicate with cannabinoid products	NA
Polito 2018 (32)	Canada	Observational; Retrospective study	Children	CINV	110	Only those who had received a dose of nabilone before the administration of the first chemotherapy dose of a chemotherapy block were eligible	December 2010 - November 2015; 5 Years

Doherty 2020 (34)	Canada	Observational; Retrospective medical record review	Children	Palliative Care	21	Children with life-limiting conditions who received medically prescribed oral cannabis extracts	January 2010-December 2018; 8 years
Warren 2017 (37)	USA	Observational: Case report	Youth	Brain tumour-related epilepsy	1	NA	NA
Rower 2021(33)	USA	Observational; Retrospective medical record review	Children and adults	Cancer related symptoms	41	1 Patients aged 28 days to <27 years; 2. An inpatient cancer diagnosis code; 3. Administration of any medication classified as an antineoplastic agent	August 2016- January 2018; 1 year 5 months
Singh and Bali, 2013 (36)	Canada	Observational; Case report	Children	Acute lymphoblastic leukemia with Philadelphia chromosome mutation	1	NA	NA
Ofir 2019 (35)	Israel	Observational; Treatment Chart review	Children and young adults	Nausea and vomiting, decreased mood, disturbed sleep, and pain	50	Medical marijuana uses in children, adolescents, and young adults	January 2010 to December 2017; 7 years 11 months
Abrahamov 1995 (46)	Israel	Open-label trial	Children	CINV	8	Children with various blood cancers	2 years
Ekert 1979 (40)	Australia	Two double-blind crossover trials	Children	CINV	19	Children with various neoplastic diseases requiring chemotherapy	NA
Chang 1979 (44)	USA	Prospective randomized trial	Children and adult	CINV	15	Osteogenic sarcoma patients	August 1977 to September 1978, 1 year
Herman 1979 (43)	USA	Randomized cross over trial	Children and adult	CINV	113	Various types of cancer	NA
Einhorn 1981 (42)	USA	Random prospective double-blind cross-over study	Children and adult	CINV	80	Patients receiving combination chemotherapy for neoplastic disease	NA

Cronin 1981 (45)	USA	Open dose finding study	Children and adult	CINV	31	Patients who had nausea and vomiting following each course of their chemotherapy and who were refractory to the aggressive use of conventional antiemetic therapy (parenteral phenothiazines)	NA
Dalzell 1986 (38)	UK	A prospective randomized double blind crossover trial	Children	CINV	18	Children 17 years old or less undergoing emetogenic antineoplastic chemotherapy for malignant disease	16 months
Chan 1987 (43)	Canada	Randomized, double blind, crossover trial	Children	CINV	30	Children treated with chemotherapy for various pediatric malignancies	February 1982 to April 1983
Sallan 1980 (41)	UK	Randomized, double blind, crossover trial	Children and adult	CINV	84	Patients known to have neoplasms	NA

Abbreviations CNS Central Nervous System, CINV Chemotherapy Induced Nausea and Vomiting, NA Not Available, UK United Kingdom, USA United States of America

Table 2.2.2. Characteristics of study participants in the included observational studies.

Author	Age	Gender	Intervention	Dose, Formulation	Frequency, Route	Type of cancer	Detailed Indication	Primary Objective
Skrypek 2019 (8)	Median: 15.3 years, Range: 1.4-28.7 years	Male: 57 (56%), Female: 44 (44%)	Medical cannabis	NA	NA	Brain Tumors: 37 (36.6%); Leukemia and Lymphoma:36 (35.7%); Solid Tumors: 26 (25.8%); Mast cell activation: 2 (1.09%)	Chemotherapy-related nausea, pain, and cancer cachexia.	To provide demographic data on our patients certified for medical cannabis
Elder 2015 (31)	Mean ± SD: 13.9 ± 3.2 years	Male: 30 (52%); Female: 28 (48%)	Dronabinol	NA	Scheduled: 30 (55%); PRN (as needed): 25 (45%); Oral route	Lymphoma: 21 (36%); Leukemia:9 (16%); Sarcoma: 21 (36%), Brain Tumor: 5 (9%), Miscellaneous: 2 (3%)	CINV	This study retrospectively evaluated the use of dronabinol in a large academic pediatric cancer center, with the intent of characterizing its use and identifying trends such as age, sex, oncology diagnosis, and chemotherapy agents that might best be administered with dronabinol as an adjuvant antiemetic
Anderson 2019 (47)	Median:59 years; Range: 48-66 years	Male: 579 (52%); Female: 534 (48%)	Medical cannabis	NA	NA	All type of cancer	Anxiety: 1029 (91.9); Appetite Lack: 1000 (89.9%); Depression: 990 (88.4%); Disturbed Sleep: 1073 (95.8%); Fatigue: 1113 (99.4%); Nausea: 923 (82.4%); Pain: 1086 (97%); Vomiting: 596	To report changes in symptom severity reported by patients with cancer during their first 4 months of program participation

							(53.2%)	
Dorris 2018 (30)	Median: 6.6 years; Range: (3.3-7.3 years)	Male: 13; Female: 13	Cannabinoids	NA	NA	Glioma: 6	CNS tumors and supportive care	To evaluate cannabinoids' impact on quality of life using PedsQL™ 4.0 modules of pediatric CNS tumor patients who self-medicate with cannabinoid products
Polito 2018 (32)	Median: 14 Years; Range: 1.1-18 years	Male: 65; (59%) Female: 45 (41%)	Nabilone	NA	NA	Solid Tumor excluding brain: 47 (42.7); Leukemia: 28 (25.5%); Brain tumor: 16 (14.5%); Lymphoma: 15 (13.6); Other 4 (3.6%)	Chemotherapy induced vomiting prophylaxis	To describe the safety and efficacy of nabilone given to pediatric patients to prevent acute chemotherapy-induced nausea and vomiting
Doherty 2020 (34)	Mean: 8.3 years; Range: 3.6 months-19 years	Male: 10 (48%); Female: 11 (52%)	Cannabis Herbal Extract	NA	NA	CNS tumor: 5 (24%); Solid tumors: 2 (10%); Hematological Malignancies: 2 (10%); Others: 1 (5%)	Treatment related epilepsy: 11 (52%); Pain: 4 (19%); Nausea/vomiting: 3 (14%); CINV: 1 (5%); Cancer: 3 (14%); Anorexia: 3 (14%); Insomnia: 1(5%)	We describe the patterns of use of oral cannabis extracts for children with life-limiting or terminal illnesses, including indications for use, observed benefits, and adverse effects
Warren 2017 (37)	Patient 1: 17 years	Male: 1	Cannabidiol	5 mg/kg/day-20 mg/kg/day	NA	Oligodendroglioma	CNS tumor related epilepsy	To examine the safety and efficacy of pharmaceutical grade cannabidiol (CBD; Epidiolex, GW Pharmaceuticals) in those patients with epilepsy with concomitant tumors

								enrolled in The University of Alabama at Birmingham CBD Program
Rower 2021(33)	Median: 12 Years; Range: 8.8–15 years	Male: 17 (41.5%); Female: 24 (585.5%)	Dronabinol	NA, capsules	NA, Oral	Leukemia/lymphoma: 26 (63.4%); CNS neoplasm 1 (2.4%); Neuroblastoma 1 (2.4%); Sarcoma 2 (4.9%); Renal 2 (4.9%); Bone 9 (22%)	Cancer related symptoms	This study evaluated national level dronabinol use and assessed concentrations of THC and its primary metabolites in patients with cancer <27 years of age prescribed dronabinol
Singh and Bali, 2013 (36)	Patient 1: 14 Years	Female: 1	Cannabis Herbal Extract	One drop up to three times a day, Oil	TDS, Oral	Acute lymphoblastic leukemia with a Philadelphia chromosome mutation	Cancer; Acute lymphoblastic leukemia	Case study is on a 14-year-old patient diagnosed with a very aggressive form of ALL (positive for the Philadelphia chromosome mutation)
Ofir 2019 (35)	Median: 13 years; Range: 7months- 21 years	Male: 31 (62%); Female: 19 (38%)	Medical Cannabis	NA; Oil drops: 30 (60%), Smoking: 11 (22%), Oil drops + Smoking: 6 (12), Capsule: 2 (4%), Smoking + Vaporizatio n: 2 (4%)	NA, Oral	Leukemia: 10 (20%), Brain tumor: 9 (18%), Sarcoma: 21 (42%), Neuroblastoma: 7 (14%), Wilms tumor: 1 (2%), Carcinoma: 1 (2%), Lymphoma: 1 (2%)	Pain 15 (30) Nausea and vomiting 8 (16) Sleep 8 (16) Appetite 15 (30) Mood 2 (4)	We present our experience using MM for children, adolescents, and young adults in the department of pediatric hematology & oncology

Abbreviations ALL Acute Lymphocytic Leukemia, CBD Cannabidiol, THC Tetrahydrocannabinol, CNS Central Nervous System, CINV Chemotherapy Induced Nausea and Vomiting, NA Not Available, PedsQL Pediatrics Quality of Life

Table 2.2.3. Characteristics of study participants in the included interventional studies.

Author	Age	Sex	Intervention	Control	Dose, Formulation	Frequency, Route	Type of cancer	Detailed Indication	Primary Objective	Major efficacy finding
Abrahamov, 1995 (48)	Mean: 6.4 years, Range: 3-13 years	Male: 4, Female: 4	delta-8 THC	NA	18 mg/m2, Oil	2 hours before chemotherapy and repeated every 6 hours for 24 hours, Oral	Hematologic cancer	CINV	The present study is on prevention of vomiting due to antineoplastic therapy with delta-8-THC	Nausea and vomiting were completely cured in all patients
Ekert 1979 (42)	Median: 11 years, Range 5-19 years	Male: 15, Female: 4	delta-9 THC	Study 1: Metoclopramide, Study 2: Prochlorperazine	10 mg/m2, Maximum dose: 15 mg, Capsules	2 hours before chemotherapy, followed by 4,8, 16 and 24 hours before chemotherapy, Oral	Unspecified cancer	CINV	To compare antiemetic properties of THC were compared with those of metoclopramide and prochlorperazine in two double blind studies	THC appeared a superior antiemetic agent, Episodes of Nausea: Study 1, delta-9 THC: 6, metoclopramide: 21. Study 2: Nausea: delta-9-THC: 6, prochlorperazine: 18; Episodes of vomiting: Study 1, delta-9 THC: 1, metoclopramide: 10; Study 2: vomiting: delta-9-THC: 18, prochlorperazine: 18
Chang 1979 (46)	Median 24 years, Range 15-49 years	Male: 10, Female: 5	delta-9 THC	Placebo	10 mg/m2, Cigarettes and capsules	2 hours before chemotherapy, every three hours, five doses in total, Inhalational and oral	Osteogenic sarcoma patients receiving high dose methotrexate	CINV	Purpose of study was to examine in a randomized, double-blind, placebo-controlled trial the efficacy of oral and smoked THC	delta-9-THC was effective than placebo in reducing episodes of vomiting, retching, degree of nausea, duration of nausea -volume of emesis

									as an antiemetic.	
Herman1979 (45)	Median: 33 years, Range: 15-74 years	Male: 126, Female: 26	Nabilone	Prochlorperazine	2 mg, capsules	Two hours before chemotherapy followed by every six hours beginning 30 minutes before chemotherapy, Oral	Unspecified cancer	CINV	To test the antiemetic efficacy of nabilone for use in cancer patients	Partial response (Nabilone vs prochlorperazine): 72% vs 32% (p <0.01), severity of nausea was also lower in nabilone group
Einhorn et al, 1981 (44)	Median: 28 years, Range: 15-74 years	NA	Nabilone	Prochlorperazine	2 mg, capsules	30 minutes before chemotherapy followed by every 6 hours, Oral	Unspecified cancer	CINV	To evaluate nabilone in a random double-blind clinical trial as compared to prochlorperazine in the treatment of chemotherapy-induced nausea and vomiting	Mean nausea score (nabilone vs prochlorperazine): 0.93 Vs 1.38; frequency of vomiting (nabilone vs prochlorperazine): 1.12 vs 2.97

Cronin 1981 (47)	Median: 33 years, Range: 11 – 68 years	Male: 15, Females: 16	Levonantradol, a synthetic derivative of THC	NA	0.5 mg to 2.5 mg, injection	2 hours prior to chemotherapy followed by 0.5 mg increment after every 4 hours, Intramuscular	Unspecified cancer	CINV	To report the initial results of a phase I-II open-dose clinical trial of levonantradol given to patients receiving chemotherapy for cancer who were refractory to conventional antiemetic therapy	Complete response (no nausea and vomiting): 89%
Dalzell 1986 (40)	Range: 10 months – 17 years	NA	Nabilone	Domperidone	<18 Kg: 0.5 mg twice a day, 18-36 kg 1 mg twice a day, > 36 kg: 1 mg three times a day, Capsules	Twice a day and three time a day	Rhabdomyosarcomas (10), Ewing's tumours (5), Acute non-lymphocytic leukaemia (4), Hodgkin's disease (1), a Medulloblastoma (1), Neuroblastoma (1)	CINV	To compare performance of nabilone with domperidone	Mean number of vomits: - (nabilone vs domperidone): 5.94 Vs 16.72, Mean severity of nausea: - (nabilone vs domperidone): 1.50 vs 2.50

Chan 1987 (43)	Mean: 11.8 years, Range: 3.5 to 7.8 years	NA	Nabilone	Prochlorperazine	61- 110 microgram/kg, capsules	Eight to 12 hours preceding to chemotherapy	Unspecified cancer	CINV	To study the antiemetic efficacy of nabilone compared to prochlorperazine in the pediatric age group	Overall rate of improvement of retching and emesis: - Nabilone vs Prochlorperazine: 70% vs 30%
Sallan 980 (41)	Mean: 32.5 years, Range: 9 to 70 years	Male: 52, Female: 33	delta-9-tetrahydrocannabinol	Prochlorperazine	10 mg per square meter of body-surface area, if weight less than 1 m square: 10 mg	First dose administered one hour before chemotherapy, other two doses three hour and four hours after chemotherapy	Unspecified cancer	CINV	To compare the effects of orally administered THC with the effects of prochlorperazine antiemetics on nausea and vomiting in patients receiving chemotherapy for cancer	Complete response (No nausea and vomiting): (delta-9 tetrahydrocannabinol vs prochlorperazine): 36/79 (45.5%) vs 16/78 (20.51%)

Abbreviations: CINV Chemotherapy Induced Nausea and Vomiting, CBD Cannabidiol, THC Tetrahydrocannabinol, NA Not available

Table 2.2.4. Comparison of adverse events between cannabinoid and control in the included interventional studies.

Adverse events	n	Cannabinoids	Control	Chi square	I^2	RR (95% CI)	Z	P
Withdrawal due to adverse events	2	5/123	1/123	0.02	0%	3.67 (0.61-1.89)	1.43	<0.001
Somnolence	4	114/177	59/141	2.59	0%	1.51 (1.23-1.84)	4.03	<0.001
Increase in appetite	2	7/50	0/50	0.49	0%	8 (1.03-61.84)	1.99	0.05
Development of high	3	67/221	7/221	1.52	0%	9 (4.38-18.48)	5.99	<0.001
Dizziness	3	104/171	36/171	6.52	69%	5.47 (1.23-4.26)	2.23	0.03
Dry mouth	2	95/135	39/135	0.02	0%	2.42 (1.85-3.16)	6.48	<0.001

2.2.13 Supplementary material

2.2.13.1 eTables

eTable 2.2.1. Cannabis-related adverse events reported by the included observational studies.

Reported adverse effects	Anderson 2021 (n= 1120)	Polito 2018 (n=110)
Drowsiness	2.5 %	20%
Dry mouth	2.2 %	NA
Fatigue	1.9%	NA
Increased appetite	1.5%	NA
Dizziness	1.3%	10%
Foggy Brain	1.3%	NA
Nausea	1.1%	NA
Headache	0.9%	2.7%
Euphoria	0.6%	3.6%
Light-headedness	0.6%	NA
Constipation	NA	2 %
Abdominal Pain	NA	1.8%
Tachycardia	NA	1.8%
Others	NA	8.2%

eTable 2.2.2. Quality assessment of the included studies using the NIH quality assessment tool for case series.

Major Components	Skrypek 2019	Elder 2015	Anderson 2021	Dorris K et al., 2018	Polito 2018	Doherty 2020	Warren 2017	Rower 2020	Singh 2013	Ofir R 2019
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes
4. Were the subjects comparable?	No	No	Yes	Yes	Yes	Yes	No	Yes	NA	Yes
5. Was the intervention clearly described?	No	Yes	No	No	Yes	No	Yes	Yes	Yes	No
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes
7. Was the length of follow-up adequate?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes

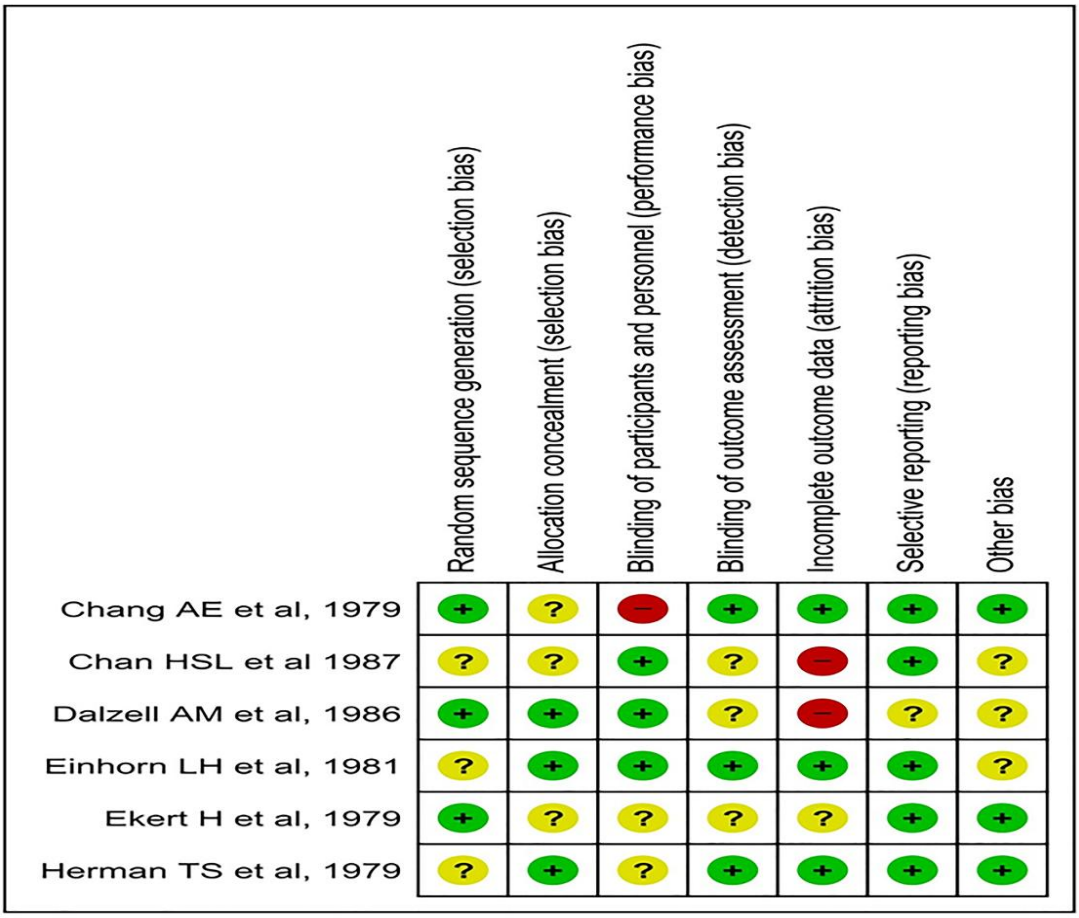
8. Were the statistical methods well-described?	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes
9. Were the results well-described?	Yes	Yes	yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Quality Rating	Good	Good	Good	Poor [a]	Good	Good	Poor [b]	Good	Fair	Good

a Result were not reported properly as it was a conference abstract limited information was present, b Only one patient was < 18 years of age and rest of them were >18 years and results were presented as separate without any uniformity

eTable 2.2.3. Quality assessment of the included open label studies using the JBI critical appraisal checklist for quasi-experimental studies.

JBI critical appraisal checklist for quasi-experimental studies	Abrahamov 1995	Cronin 1981
1. Is it clear in the study what is the cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes	Yes
2. Were the participants included in any comparisons similar?	Not applicable	Not applicable
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Not applicable	Not applicable
4. Was there a control group?	No	No
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	No	Yes
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Yes
7. Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes
8. Were outcomes measured in a reliable way?	Yes	Yes
9. Was appropriate statistical analysis used?	Yes	Yes

2.2.13.2 eFigure



eFigure 2.2.3. Risk of bias graph for the included randomized controlled trials.

2.2.13.3 Search Strategy

2.2.13.3.1 Multifile Ovid Search

Embase <1974 to 2022 April 26>

Ovid MEDLINE(R) ALL <1946 to April 26, 2022>

APA PsycInfo <1806 to April Week 3 2022>

1 Cannabis/

2 exp Cannabinoids/

3 Cannabaceae/

4 Medical Marijuana/

5 Marijuana Use/

6 Marijuana Smoking/

7 cannab*.tw,kf.

8 Mari?uana*.tw,kf.

9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw,kf.

10 (19GBJ60SN5 or 2N4O9L084N or 7J8897W37S or K4H93P747O).rn.

11 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta(9)tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw,kf.

12 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kf.

13 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kf.

14 or/1-13 [CANNABIS CONCEPT]

15 exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. [CHILDREN CONCEPT]

16 14 and 15

17 exp Animals/ not (exp Animals/ and Humans/)

18 16 not 17 [EXCLUDING ANIMAL ONLY STUDIES]

19 (202106* or 202107* or 202108* or 202109* or 20211* or 2022*).dt,ez,da.

20 18 and 19

21 20 use medall

22 cannabis/

23 exp cannabinoid/

24 cannabaceae/

25 exp "cannabis (genus)"/

26 medical cannabis/

27 exp "cannabis use"/

28 cannab*.tw,kw.

29 Mari?uana*.tw,kw.

30 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw,kw.

31 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta(9)tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw,kw.

32 (8063-14-7 or 1972-08-3 or 13956-29-1 or 51022-71-0 or 8001-54-5 or 33086-25-8 or 36557-05-8 or 24359-49-7).rn.

33 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kw.

34 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kw.

35 or/22-34

36 exp child/ or exp newborn disease/ or exp infant/ or exp adolescent/ or exp pediatrics/ or abandoned child/ or gifted child/ or orphaned child/ or unwanted child/ or "minor (person)"/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

37 35 and 36

38 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

39 Animal experiment/ not (human experiment/ or human/)

40 38 or 39

41 37 not 40

42 limit 41 to dc=20210617-20220427

43 42 use oemezd

44 exp cannabis/

45 exp cannabinoids/

46 marijuana/

47 marijuana usage/

48 marijuana legalization/

49 cannab*.tw.

50 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw.

51 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta(9)tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw.

52 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw.

53 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw.

54 or/44-53 [Cannabis Concept]

55 limit 54 to (childhood <birth to 12 years> or adolescence <13 to 17 years>)

56 exp pediatrics/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

57 54 and 56

58 55 or 57

59 exp Animals/ not (exp Animals/ and Humans/)

60 58 not 59

61 limit 60 to up=20210617-20220427

62 61 use psyc17

63 61 use psyc18

64 61 use psyc16

65 or/62-64

66 21 or 43 or 65

67 remove duplicates from 66

**Note Ovid multifile search of MEDLINE, Embase, and PsycInfo was run on June 20, 2020, June 17, 2021, and April 27, 2022. The search remains unchanged except for date limits.*

2.2.13.3.2 Cochrane Library (Wiley) Search Strategy

ID Search Hits

#1 MeSH descriptor: [Cannabis] this term only

#2 MeSH descriptor: [Cannabinoids] explode all trees

#3 MeSH descriptor: [Cannabaceae] this term only

#4 MeSH descriptor: [Medical Marijuana] this term only

#5 MeSH descriptor: [Marijuana Use] explode all trees

#6 MeSH descriptor: [Marijuana Smoking] this term only

#7 cannab*:ti,ab,kw

#8 Mari?uana*:ti,ab,kw

#9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla):ti,ab,kw

#10 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta(9)tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex):ti,ab,kw

#11 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726"):ti,ab,kw

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 MeSH descriptor: [Child] explode all trees

#14 MeSH descriptor: [Congenital, Hereditary, and Neonatal Diseases and Abnormalities] explode all trees

#15 MeSH descriptor: [Infant] explode all trees

#16 MeSH descriptor: [Adolescent] this term only

#17 MeSH descriptor: [Pediatrics] explode all trees

#18 MeSH descriptor: [Child, Abandoned] this term only

#19 MeSH descriptor: [Child, Exceptional] this term only

#20 MeSH descriptor: [Child, Orphaned] this term only

#21 MeSH descriptor: [Child, Unwanted] this term only

#22 MeSH descriptor: [Minors] this term only

#23 (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or "premature birth*" or NICU or preschool* or pre-

school* or kindergarten* or kindergarden* or "elementary school*" or "nursery school*" or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*):ti,ab,kw

#24 (child* or adolesc* or pediat* or paediat*):so

#25 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

#26 #12 AND #25 with Cochrane Library publication date Between Jun 2021 and May 2022

**Note Cochrane Library search via Wiley was run on June 20, 2020, June 17, 2021, and April 27, 2022. The search remained unchanged except for date limits and a correction in a typo between June 2020 and June 2021 in Line #11 where .ti,ab,kw was used instead of :ti,ab,kw*

Section 2.3 Cannabinoids used for symptom management in children with autism spectrum disorder: A systematic review and meta-analysis

2.3.1 Overview

In our LSR, ASD was the most common indication for cannabinoid use in children, following epilepsy and cancer. We felt a strong need to synthesize evidence on cannabinoid use in children with ASD to inform practice and research. We aimed to systematically appraise current evidence on the dosing, safety, and efficacy of cannabinoids in children with ASD.

This systematic review is a second subgroup review, synthesizing evidence from 43 studies to provide up-to-date evidence on cannabinoid use for symptom management in children with ASD. In this systematic review, we did a narrative synthesis of efficacy outcomes and pooled adverse event profiles of cannabinoid use in children with ASD.

Cannabinoids used for symptom management in children with autism spectrum disorder: A systematic review and meta-analysis

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Manuscript status

Under submission.

2.3.2 Abstract

IMPORTANCE Interest in using cannabinoids in children with autism spectrum disorder (ASD) has increased over the past decade.

OBJECTIVE We aimed to systematically appraise the current evidence on the dosing, safety, and reported benefits of cannabinoid use in children with ASD.

DATA SOURCES MEDLINE, Embase, CINAHL, PsycINFO, Cochrane Library, Web of Science Core Collection, and Google Scholar databases were searched.

STUDY SELECTION Two reviewers independently performed title, abstract, and full-text screening. Studies involving at least 1 child aged 18 years or below using pharmaceutical or phytocannabinoids for ASD-related symptom management were included.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently performed data extraction and quality assessment. R Studio was used for data analyses. Data were pooled using a random-effects model. Adverse event data from single-arm trials and observational studies was pooled as proportions.

MAIN OUTCOMES AND MEASURES Primary outcomes were the type of cannabinoids, dosing, and reported benefit of cannabinoid use in children with ASD. Secondary outcomes were the incidence of withdrawal, withdrawal due to adverse events, adverse events, serious events, and specific adverse events.

RESULTS Forty-three unique studies were identified, including 7 case reports, 3 case series, 7 cross-sectional surveys, 2 qualitative interviews, 9 observational studies, 2 treatment chart reviews, 8 single-arm trials, and 5 randomized controlled trials. Of these 43 studies, 62.7% (n=27) included children exclusively. The total number of participants in the included studies were 4330,

with an average male: female percentage ratio of 80.9:18.8. Cannabidiol (CBD)-enriched cannabis herbal extract (n=25/43, dose-range 0.9-21 mg/kg CBD/day, 0.1-0.8mg/kg THC/day), purified CBD (n=7/43, 3-20 mg/kg/day), cannabidivarin-enriched cannabis herbal extract (n=1/43,5-20 mg/kg/day), cannabidiolic acid-enriched cannabis herbal extract (n=1/43,1.5mg CBDA/day, 0.6mg THCA/day), dronabinol (n=3/43, 0.62-20 mg/day), and undefined medical cannabis (n=7/43) were used in children with ASD. Epilepsy, sleep impairment, hyperactivity, concentration impairment, and irritability were the common symptoms managed with cannabinoids in children with ASD. The pooled prevalence of adverse events (AEs) across single-arm and observational studies was 44.8% (95% CI, 24.1-67.4;I2=94%; 9 studies) in children with ASD.

CONCLUSION and RELEVANCE Due to heterogeneity in outcome selection and small sample sizes, there is insufficient data to assess the efficacy of cannabis in ASD.

Protocol registration: This systematic review was registered with Open Science Framework (https://osf.io/e6hjs)

Keywords Cannabidiol; tetrahydrocannabinol; medical cannabis; autism spectrum disorder; safety; symptom management

2.3.3 Key Points

Question What evidence is available on cannabinoid-based products used, symptoms managed, and their safety in children with ASD?

Findings In this systematic review and meta-analysis of 43 studies, including 4,330 children with autism spectrum disorder. Cannabidiol-enriched herbal extracts was the most common cannabinoid used for epilepsy, sleep, hyperactivity, concentration impairment, and irritability management in children with ASD. Cannabinoids were reported to reduce the co-administered medications and their doses in children with ASD. Validated benefit measures were reported inconsistently across studies.

Meaning Cannabinoids may be beneficial in managing symptoms in children with ASD, but there is insufficient data supporting its use in children with ASD. There is need to conduct high quality clinical research evaluating safety, and benefits of medical cannabis in children with ASD.

2.3.4 Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder that occurs frequently in children.(1) Globally, one in 100 children is diagnosed with ASD, with more males affected than females (median male-to-female prevalence ratio of 4.2).(2) According to the Canadian Health Survey on Children and Youth (2019), approximately 1 in 50 Canadian children (aged 1-17 years) were diagnosed with ASD.(3) In the United States, the Autism and Developmental Disabilities Monitoring Network active surveillance program reported an even higher prevalence of ASD at 27.6 per 1,000 children (1 in 36) aged 8 years.(4)

The deficits caused by ASD are multifactorial and include disruptions in social communication, interaction, and cognitive function with repetitive and restrictive behaviour.(1) ASD can present with differing degrees of severity ranging from mild to severe. Children with ASD can experience intellectual disabilities, behavioural and language problems, irritability, difficulties in social communication, and struggle to detect facial expressions and adapt their responses, including regulating volume or distance to communicate.(5) Attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, epilepsy, and sleep-related disorders are common co-morbidities experienced by children with ASD.(5) Behavioral interventions (early intensive behaviour intervention and discrete trial training) are the current standard of care to manage children with ASD.(1)

To date, no single pharmacological option exists to manage all core autism-related including social communication challenges, restricted and repetitive behavior as well as speech impairment, and language delays in children.(6, 7) Risperidone and aripiprazole (atypical antipsychotics) are the only US Food and Drug Administration-approved medications for irritability and aggression in children with ASD.(7) However, these medications are associated

with negative effects, such as weight gain, hyperglycemia, and dyslipidemia.(7) Atomoxetine,(8) guanfacine(9) and methylphenidate(10) have shown promising results for ADHD management in children with ASD, but they are associated with negative effects such as decrease in appetite, sleep disturbances, and headache.(9, 11) Owing to the lack of available therapeutic options and continued behavioural challenges, families have shown considerable interest in using cannabis herbal extracts (CHEs) containing cannabinoids in their children with ASD.(12-14) As such, research exploring the therapeutic potential of cannabinoids in children with ASD has also expanded in the past decade.(15-20)

Cannabinoids act through the endocannabinoid system, which comprises of cannabinoid 1 and 2 receptors, endocannabinoids, and enzymes responsible for the synthesis and degradation of endocannabinoids.(21) Cannabinoid 1 (CB1) receptors are expressed in the brain, while CB2 receptors are expressed in immune cells and peripheral tissues. They are essential in regulating electrical impulses, pain, mood, sleep, appetite, and immune functions in the body.(22) Preclinical (animal) and clinical (human) studies report dysregulation of the endocannabinoid system in ASD with changes in the expression of cannabinoid receptors in the periphery (23) and blood cells.(23) Lower plasma levels of anandamide, *N*-oleoyl ethanolamine and N-palmitoyl ethanolamine are also reported in children with ASD compared to healthy controls.(24) In ASD-related preclinical models, alteration of endocannabinoid signalling resulted in improvement in social impairment in adult male BTBR mice with ASD-like features.(25) In 2020, a scoping review summarized eight completed and five ongoing studies on cannabinoid use for symptom management in children with ASD; however, a critical appraisal of included studies was not performed.(26) Since then, a mounting number of studies have explored the therapeutic potential of cannabinoids in children with autism. We conducted a systematic review to map recent

evidence on cannabinoids used for symptom management in children with ASD to inform clinical practice and future clinical research.

2.3.5 Methods

This systematic review was registered with the Open Science Framework (OSF),(27) and we used the Cochrane Collaboration guidelines(28) to conduct this systematic review and the preferred reporting items for the systematic review (PRISMA) checklist(29) and PRISMA-S(30) to ensure complete and accurate reporting.

2.3.5.1 Eligibility criteria and outcomes

The research question for this review was *"What evidence is available on cannabinoid-based products used, symptom managed, and their safety in children with ASD?"* We included studies in which at least one child aged 18 years or younger used pharmaceutical cannabinoids or phytocannabinoids for management of ASD-related symptoms. All study designs that described medical cannabis use in ASD were considered, randomized controlled trials (RCTs), single-arm trials, cohort studies, case-control studies, cross-sectional studies/surveys, qualitative interviews, treatment chart reviews, case series, and case reports published as full texts or conference abstracts. Interventions included studies where phytocannabinoids or pharmaceutical cannabinoids, or both, were used for symptom management in children with ASD. This included self-reported cannabis product use, whether or not it was under the supervision and authorization of healthcare professionals. Cannabidiol (CBD), tetrahydrocannabinol (THC), plant-based extracts of cannabidiol (CBD) or THC, nabilone, dronabinol, dexanabinol, levonantradol, tetrahydrocannabinolic acid (THCA), cannabidiolic acid, and cannabidivarin were included in this review. Studies satisfying the criteria mentioned above and reporting any of the following outcomes. Primary outcomes including type of cannabinoid, dosing, formulation, frequency of

administration, symptoms managed, all reported benefit of cannabinoid use in children. Secondary outcomes include adverse events, withdrawals, withdrawals due to adverse events, and specific adverse events in cannabinoid and control groups or cannabinoids only for single-arm or observational studies. Expert opinions, letters to the editor, reviews, and studies on accidental ingestion of cannabinoids or where cannabinoids were used for recreational purposes were excluded.

2.3.5.2 Search strategy

This is an updated and secondary data analysis of a living systematic review of pediatric medical cannabis use (CRD42020187433) completed by a health sciences librarian (ML). We used the previous search, except for the added search concept of autism spectrum disorder (ASD). The new search strategy was peer reviewed by another health sciences librarian (EL) using PRESS.(31) An experienced health sciences librarian (CP) searched MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), PsycINFO (EBSCO), Cochrane library, Web of Science Core Collection, and Google Scholar. Grey literature was sought from the World Health Organization, International Clinical Trials Registry Platform, ClinicalTrials.gov, Scopus conference abstracts, Papers First (OCLC), Proceedings First (OCLC), ProQuest Dissertations & Theses Global, and the Networked Digital Library of Theses and Dissertations. Searches were limited by the last search date for each source, where applicable. The search was not limited by language. Forward and backward citation searching of all included studies was completed using Scopus. We also searched the references of relevant evidence synthesis reviews, including systematic and scoping reviews.

2.3.5.3 Study selection and data extraction

First-pass screening (title and abstract), second-pass screening (full text), data extraction, and quality assessment were independently performed by two reviewers (MC, CP, or EL) in duplicate. Any disagreements were resolved by consensus among reviewers or by contacting a third reviewer (LEK). Data extraction was performed based on the characteristics of the included studies, study participants, and reported efficacy and safety outcomes. The characteristics of the included studies and participants included study design, study center, location, inclusion criteria, exclusion criteria, ASD diagnostic criteria, sample size, number in each arm, cannabinoid dose, frequency, route of administration, duration of the study (duration of treatment and safety follow-up), comorbidities, and concomitant drugs. All efficacy outcomes reported by the included studies were considered because of the large variability in the outcome assessment scales used across the included studies. The safety outcomes included withdrawal, withdrawal due to adverse events, adverse events, serious events, and specific adverse events. The critical appraisal of included studies was done using following tools: the Cochrane risk of bias (ROB) tool (for RCTs),(32) Joanna Briggs Institute (JBI) checklist for quasi-experimental design (non-randomized experimental studies),(33) JBI checklist for prevalence studies (cross-sectional studies),(34) JBI checklist for qualitative research,(35) JBI critical appraisal checklist for case series(36) and JBI critical appraisal checklist for case reports.(37)

2.3.5.4. Data synthesis

R studio (RStudio-2024.04.2-764.exe) was used to pool adverse event data with 95% Confidence Interval (CI) using the Der Simonian and Laird method for the random-effects model. Binary adverse event data from the RCTs was pooled as Risk Ratios (RRs) with the help of “metabin” packages. Adverse event data from single arm trials and observational studies was

pooled as proportions using metabin package.(38) I^2-statistics was used to explore statistical heterogeneity.(39) Further, subgroup analysis based on the study design and type of cannabinoid was conducted to explore sources of heterogeneity. Descriptive synthesis of non-quantitative outcomes was performed using the synthesis without meta-analysis guidelines.(40)

2.3.6 Results

Forty-three unique studies were included: 7/43 (16.27%) single patient case reports (7 participants)(15, 41-46) 3/43 (6.97%) case series (n=20 participants)(47-49), 2/43 (4.65%) chart reviews (n=41 participants) (50, 51), 7/43 (16.27%) cross-sectional surveys (n=3002 participants)(13, 14, 16, 52-55), 2/43 (4.65%) qualitative interviews (n=35 participants) (12, 56), 9/43 (20.93%) observational studies (n=268 participants)(57-65), 8/43 (18.60%) single arm trials (n=318 participants)(17, 18, 66-71), and 5/43 (11.62%) RCTs (n=284 participants).(19, 20, 72-74) **Figure 2.3.1.** shows the PRISMA diagram of the included studies.

2.3.6.1 Characteristics of included studies

Characteristics of included studies varied broadly. Most were single center: except 2 cross-sectional surveys,(16, 54) 1 observational study,(58) and 1 single-arm study (70); 14/43 (32.55%) were from the USA: 6 cross-sectional surveys,(13, 14, 16, 52-54) 2 single-arm trials(66, 69), and 1 each case report(15), qualitative interview(12), case series(47), treatment chart review(51), observational study(64), and RCT(73); 7/43 (16.27%) studies were from Brazil: 1 each case series(48), and RCT (20), followed by 2 case reports(43, 44), and 3 observational studies(61-63); 8/43 (18.60%) from Israel: 1 cross-sectional survey(55), 3 observational studies(57-59), 3 single-arm trials(17, 18, 71), and 1 RCT(72); 6/43 (13.95%) from Australia: 1 case series(49), 3 single-arm trials(67, 68, 70), and 2 RCTs(74),(19); 3/43 (6.97%) from Canada: 2 case reports(42, 45), and 1 qualitative interview(56); and 1/43 (2.32%) each

from Austria (1 case report(41)), Italy (1 case report(46)), Chile, (1 treatment chart review (50)), Switzerland (1 observational study(65)) and Turkey (1 observational study (60)). Average male to female study participants in the included studies were 80.9:18.8% (8 studies did not report on sex). The duration of the included observational studies ranged from 1 month to 24 months, whereas in interventional studies, the duration ranged from 1 month to 6 months. Twenty-four studies exclusively focused on children with autism as study participants.(15, 19, 20, 41, 42, 44-46, 48, 51, 54, 57, 58, 60-62, 64-70, 73) Each case report(43) and case series(47) included adults with autism using cannabis herbal extracts to treat autism-related symptoms since their childhood. **Table 2.3.1.** describes the complete characteristics of the included studies and participants.

Four of the 7 included case reports had a higher risk of bias.(15, 43, 44, 46) Patient demographic details were unclear in 2 case reports.(43, 46) Details on post-intervention clinical conditions were missing in 2 case reports.(43, 44) High and unclear risk of bias were present in 5(48, 49, 51, 60, 62) and 3(47, 50, 64) studies assessed with the JBI checklist for case series. Demographic details were missing and unclear in 4(48, 49, 51, 60) and 3 observational studies.(50, 62, 64) In qualitative studies, 1 had a low risk of bias(56) and other had an unclear risk of bias.(12) Three cross-sectional surveys had a high risk of bias due to the lack of description of study subjects (2 surveys),(14, 52) and a low response rate (2 surveys).(14, 16) In 2 single-arm trials with high risk of bias there was lack of follow-up of children with ASD receiving cannabinoids.(68, 70)On the Cochrane ROB tool, an unclear and high risk of bias (2 RCTs were conference abstracts) was present in 2(19, 73) and 1(20) included RCTs. In a high risk of bias RCT, there was no allocation concealment and incomplete reporting of outcome

data.(20) **eFigures 2.3.1., 2.3.2., 2.3.3., 2.3.4., 2.3.5., and 2.3.6.** illustrate a complete summary of the quality assessment of the included studies.

2.3.6.2 Cannabinoids and dosing

CBD-enriched cannabis herbal extract (CHE) was used in 25/43 included studies (58.13%; 6 case reports(15, 42-47), 3 case series(47-49), 1 cross-sectional survey(16), 1 qualitative interview(56), 8 observational studies(50, 57-63) , 2 single-arm studies(17, 18), 3 RCTs(20, 72, 74)) with a dose range of 0.9-21 mg /kg CBD/day (>40 kg maximum 420mg CBD/day) and 0.1-0.8mg/kg THC/day (>40 kg maximum 21 mg THC/day) in children with ASD. CBD: THC ratios in CBD-enriched CHE products used in children with ASD were 1:20,(18, 42, 45, 56, 57, 59, 72) 1:9,(20) 5.71:3.07,(63) 1:1(50), 75:1,(61) 30:1.5(58), 15:0.7(56), 100:1(48), 100:0.3(43). One identified randomized cross-over trials used both purified CBD and CBD-enriched CHE in children with ASD.(72) Purified CBD was used in 7/43 included studies (16.27%; 1 qualitative interview,(56) 3 single arm trials(66, 68, 70), 3 RCTs(19, 72, 73)) with a dose range of 3-20 mg/kg CBD/day (>25 kg maximum 500-1000 mg CBD/day) in children with ASD. In 3/43 included studies (6.97%; case report(41), observational(65), and single arm trial(69)) with a dose range of 0.62-20 mg/day in children with ASD. Cannabidiolic acid (CBDA)-enriched CHE (CBDA 1.5 mg/day, THCA 0.6 mg/day) and cannabidivarin (CBDV)-enriched CHE (5-20 mg/kg/day) were used in a case report(44), and single-arm trial(67), respectively. Cannabinoid types or doses and CBD THC ratios were not specified in 11/43 studies (25.5%).

2.3.6.3 Safety

In observational and single-arm trials, the pooled proportion of cannabinoid-related adverse events in children with autism was 44.8% (95% CI, 24.1-67.4; $I^2 = 94\%$; 9 studies). To

address the heterogeneity of 94%, a subgroup analysis was conducted based on cannabinoid type and study design. Purified CBD (89.2%; 95% CI, 57.8- 98.0; $I^2 = 80$; 2 studies) and CBD-enriched CHE (41.1%;23.7- 61%; $I^2 = 0\%$; 3 studies) reported a higher proportion of cannabinoid-related adverse events in children with ASD. Based on study design, single-arm trials (89.2%; 95% CI, 57.8- 98.0; $I^2 = 80\%$; 2 studies) reported a higher proportion of cannabinoid-related adverse events. The proportions of withdrawals, withdrawals due to adverse events, and cannabinoid-related serious adverse events in the observational and single-arm trials were 19.6% (95% CI, 13.7-27.3; $I^2 = 73\%$; 11 studies), 7.4% (95% CI, 3.9-13.4; $I^2 = 71\%$; 8 studies), and 7.4% (95% CI, 0.6-50.9; $I^2 = 84\%$; 2 studies), respectively. Specific cannabinoid-related AEs with a pooled proportion >10 reported by observational and interventional studies include restlessness, somnolence, and tiredness. **Table 2.3.2.** describes the primary safety outcomes reported by the observational and single-arm studies.

eTable 2.3.2. presents a comprehensive list of the safety outcomes reported by observational and single-arm interventional studies. In RCTs, anxiety (23.4% vs. 13.8%), somnolence (25.5% vs. 7.4%), tiredness (29.8% vs. 19.1%), and were reported in higher proportions in the cannabinoid group. In RCTs, compared to control, cannabinoids were also associated with decrease in weight decrease (Risk Ratio, 2.89; 95% CI 1.09-7.65%; I^2 0; 2 studies) in children with ASD. **eTables 2.3.3. and 2.3.4.** present the complete safety outcomes reported in the RCTs.

2.3.6.4 Reported benefits of Cannabinoid

In case reports, cannabinoids were beneficial for ASD-related symptoms, sleep,(15, 45) attention, and learning capabilities,(15, 42, 43) as well as reducing anxiety,(42, 45) aggression,(43) self-injurious behavior,(42) panic attacks, and agitation episodes(44). In one case

report, dronabinol decreased hyperactivity by 27 points, lethargy by 25 points, and irritability by 12 points, which is clinically non-significant [assessed by the Aberrant Behavior Checklist (ABC)].(41) In two case series, CBD-enriched CHE was not helpful because of adverse events, mania, and psychosis.(47, 49) In cross-sectional surveys, irritability, aggression, agitation, communication, sleep, anxiety, eating problems, obsessions and concentration problems were the common symptoms treated with cannabinoids in children with ASD .(52, 53) In cross-sectional surveys, caregivers of children with autism reported moderate effectiveness of cannabinoids for treating behavior of interest in children.(16)

In observational studies, CBD-enriched CHE reported improvement in the clinical global impression-caregiver (CGI-C) score of ≤ 2 (37/60 children).(50, 57) Hyperactivity (26/38 children),(59) seizures (>50% reduction 5/5 children),(61) mood,(51) self-injury, sleep problems, anxiety (8/17),(59) ADHD;(62) additionally, stereotype behavior(60) were the co-morbidities improved with cannabinoids; additionally, improvement in language, cognition, and social interaction were also reported.(50) Cannabis-based products were also reported to improve Autism Parenting Stress Index (APSI) scores by 66.7% in one observational study.(50) In another study the median improvement in APSI was 0.66 ± 0.74 in another study.(57) In a single-arm trial, CBD-enriched CHE significantly improved parent reported restricted and repetitive behaviour in children with ASD, with mean ±SD change of 4.37 ±1.18 in CHSQ scores.(17) Dronabinol in single-arm trial was reported to improve self-injurious behaviour and overall well-being in 7/10 participants.(69) Responders (CGI-Investigator ≤ 2) in single-arm trials were ranging between 42% to 77%,(66-68) while in RCTs responders in the cannabinoid group versus placebo group were 43.3% versus 21.7%.(72) CBD-enriched CHE in a single arm trial reported improvements in social communication (mean change in Autism Diagnostic Observation

Schedule: 0.56 ± 0.17, and social responsiveness scale: -3.29 ± 1.13), but there were no changes in cognition scores.(17)

The reduction in ABC-Investigator and APSI score in cannabinoid group versus placebo in RCTs were 12±2.1 versus 2.5±0.4 and 8.6 ±1.9 versus 4.5±1.6, respectively.(72) In RCTs, CBD-enriched CHE treatment was associated with improvements in aggressivity, psychomotor agitation, concentration, social interaction, and stereotypy behaviour.(20)

2.3.7 Discussion

Research on the use of cannabinoids in children with ASD is rapidly evolving. This systematic review summarizes evidence from 43 studies on cannabinoids for symptom management in children with ASD to inform policy, practice, and future clinical research. Parents remain frustrated with a lack of effective options to support children with ASD. In cross-sectional surveys and qualitative studies, parents of children with ASD showed interest in using cannabinoids for symptom management in their children,(12-14, 16, 52-54, 56) and social media as well as internet were reported as the major sources of information.(14) Parents reported accessing unlicensed cannabis products from recreational markets in the form of oils, gummies, drops, tinctures, lotions, and lollipops.(13) Parents also report preparing CHE themselves at home for their children with ASD.(44) This is concerning as cannabinoids can interact with other drugs and should be administered under the supervision of healthcare practitioner.(75) To support shared decision making, healthcare practitioners should create plans for open and unbiased discussions with families planning to use cannabinoids in children with ASD.

Product selection in ASD remains a challenge as international regulations control what cannabis-based products are available for purchase and for use in research in each jurisdiction.

CBD-enriched CHEs containing different amount of THC, Purified CBD,(19, 73) Cannabidivarin-enriched CHEs, (67) Cannabidiolic acid-enriched CHE,(44) dronabinol, (69) and undefined medical cannabis(15, 48) were cannabinoids used in children with ASD. We also reported that products containing cannabinoids were used in different ratios, and 11/40 (27.5%) studies did not describe the exact amounts of CBD or THC.(51, 64) Dose response relationship of cannabinoids was not explored any of included studies in children with ASD. Purified CBD and CBD-enriched CHE doses were similar to its doses used in children with refractory epilepsy.(76) Dronabinol doses were high (0.6-20 mg/day) as compared to its dose used (for management of chemotherapy induced nausea and vomiting) in interventional studies in children with cancer.(77) There are no other studies reporting CBDV(67) and CBDA use in children for medical purposes except ASD. The lack of standard definitions for reporting cannabis exposures has been reported in previous systematic reviews on cannabinoids,(26, 78) and should be addressed with a reporting standing for cannabis-based interventions. As there are no clinical practice guidelines to guide the use of cannabinoids in children with ASD, there is an urgent need for investigators across the globe to come together and interpret the data from ongoing and upcoming RCTs evaluating the safety and efficacy of cannabinoid use in children. **eTable 2.3.5**. presents a comprehensive description of ongoing studies related to cannabinoids in children with ASD.

The response of cannabinoids is quite variable, and children with ASD are no exemption. In three studies CBD-enriched CHE reported to reduce anxiety,(57) while in one study CBDV-enriched CHE increase anxiety in 36% of study participants(67) as well as in one case series there was an increase in anxiety with CBD-enriched CHE.(49) Furthermore, in two cases in two different case series, children experienced anxiety, mania, and psychosis after treatment with

CBD-enriched CHE, and their symptoms subsided upon its cessation.(47, 49) There was huge variability in cannabinoid type, composition (CBD:THC ratios), and dosing in children with ASD. Similar findings were reported in our living systematic review and previously published systematic reviews.(26, 77, 79, 80)

Importantly, cannabinoids reduced the co-administered medications and their doses in children with ASD. In an observational study, CBD-enriched CHE treatment led to reduction and complete cessation of administered medications in 26.6% and 20% of children, respectively.(57) Furthermore, in one identified case report, replacing traditional CHE with terpene-rich CHE was reported to be helpful in reducing aggression, improving speech and sense of humor. There is a paucity of research on the role of minor cannabinoid, terpene, and non-cannabinoid components in CHEs can impact efficacy and safety outcomes. Due to the huge variability in cannabinoid treatment response, there is a need for a personalized medicine approach to tailor their dosage regimens based on genomic make-up, concomitantly administered drugs, and comorbidities.

Cannabinoids were used to manage ASD-related symptoms, including aggression, hyperactivity, anxiety, epilepsy, behavioral problems, cognition, irritability, and sleep.(15, 19, 48, 57-60, 62, 63, 67, 69, 73) Epilepsy is a common comorbidity in children with ASD.(81) Purified CBD has shown promising results in managing seizures in children with refractory epilepsy and is well supported by multicenter RCTs.(78) In observational studies, cannabinoids were reported to reduce seizure frequency up to 100% in children with ASD,(61) but none of the included RCTs have explored its efficacy in reducing seizure frequency and severity in children with ASD.(19, 20, 72, 73) Cannabinoids were reported to be beneficial in improving the quality and quantity of sleep in children with ASD in observational studies,(51, 61) single-arm trials(67), and one RCT(20); observational studies were retrospective, and RCT sample size was not powered.

Cannabinoids were also reported beneficial for cognition, communication, hyperactivity, ability to perform tasks independently and school attendance in children with ASD.(19, 20, 50, 57, 58, 60, 72, 73) However, these findings were not supported by the high quality RCTs.(19, 20, 72, 73)

Cannabinoids may improve ASD-related symptoms via the endocannabinoid system(82, 83) which plays a key role in neurotransmission, synaptic plasticity, cognition, emotion regulation, and reward processing. Anandamide, and 2-achadonlyglycerol, cannabinoids produced naturally in the body (endocannabinoids) activate receptors and modulate neuronal reflexes in the body.(82, 83) The endocannabinoid system is reported to be malfunctional in children with ASD with lower levels of circulatory endocannabinoids.(24) CBD increases the level of endocannabinoids by inhibiting fatty acid amide hydrolase enzyme (which breakdowns anandamide) and decreases the degradation of 2-AG by inhibiting monoacylglycerol lipase.(84)

2.3.7.1 Quality of evidence

ASD-related outcome assessment tools used in these studies were highly subjective and lacked internal validity and reliability. A previously published scoping review(26) and systematic reviews have also reported similar issues, which jeopardize the ability to quantify, pool data, and draw conclusions on cannabinoid efficacy in children with ASD.(26, 77, 79, 80) Furthermore, this also complicates the effect size and power calculation for prospective RCTs. To the best of our knowledge, there is no published core set of outcome tools to assess the efficacy of healthcare interventions in children with ASD. The current evidence on cannabinoid use in children with ASD is not well supported by high-quality RCTs. There is a need to conduct innovative adaptive RCTs to test the safety and efficacy of cannabinoids on ASD-related core symptoms such as sleep, seizure, aggression, hyperactivity, and cognition. A scoping review conducted in 2021 reported a lack of RCTs;(26) however, we included four RCTs exploring the

safety of cannabinoids used in children with ASD. Recent Canadian pediatric society statement on medical cannabis in children also reported the need of placebo-controlled trials to draw conclusion on potential therapeutic benefits of cannabinoids in children with ASD.(85) The internal validity of 3/4 included RCTs was low, two RCTs lacked proper details due to published conference abstracts, and one trial was of high quality.(19, 20, 72, 73) The overall quality of the included studies was low; this issue was also reported in previous literature.(79, 80)

2.3.7.2 Limitations

This systematic review has limitations that impede with our ability to make any clinical recommendations. The quality of the included studies was low, and the majority were single center, limiting the generalizability of the findings. We were unable to retrieve the full texts of the published conference abstracts. Most of the included studies were retrospective observational studies, single-arm trials, with a limited number of RCTs in children with ASD identified. The sample size of the RCTs was under powered for efficacy. Retrospective and observational studies are helpful in detecting signals of safety, but they are subject to recall bias and a lack of comparator group. The outcome assessment tools used in studies lacked homogeneity, internal validation, and reliability. Furthermore, cannabinoid-related AEs reporting was not uniform with missing data on AEs' severity and causality related to cannabinoids. The included studies also did not report long-term safety data. This is a major limitation to interpreting our findings as there is a need for long-term safety data on the effects of cannabinoids on brain architecture, cognition, and psychiatry-related adverse events.

2.3.7.3 Future direction

Given the increasing global interest in the use of cannabinoids in children with ASD, there is an urgent need to develop treatment guidelines to avoid cannabinoid-related negative

effects and achieve maximum benefits. Global collaborations are warranted to design and conduct multicenter adaptive randomized controlled trials to assess the safety and efficacy of cannabinoids in children with ASD. A standardized tool for collecting cannabinoid adverse events and a core set of outcome tools related to ASD should be developed and adapted internationally. Long-term safety studies of cannabinoids in children with ASD should be conducted. The effects of cannabinoids on brain development and psychiatry-related adverse events should be studied extensively in children with ASD. Additionally, there is a need to study cannabinoid-related drug-drug interactions in children with ASD in the real world.

2.3.8 Conclusion

This systematic review of 43 studies revealed increasing interest and research on cannabinoid use in children with ASD. Cannabinoids may be beneficial in managing symptoms in children with ASD, but this is not well supported by high-quality evidence. There is a lack of evidence on the long-term safety, efficacy, and drug interactions related to cannabinoids in children with autism. Further, there is a need to develop a core set of outcome assessment tools to be used in prospective clinical research. Our systematic review highlights the need to generate high-quality evidence on safety, efficacy, dosing, and ASD-related symptoms managed with cannabinoids in children with ASD.

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2.3.10 Author contribution statement

MC Conceptualization, Methodology, Data curation, Visualization, Writing – original draft, Writing – review & editing, Data curation; **CP** Data curation, Methodology, Writing – review & editing, **EL** Data curation, Methodology, Writing – review & editing; **ML** Data curation, Writing – review & editing; **HS, SRR, TFO,** Conceptualization, Writing – review & editing; **LEK** Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Writing – review & editing.

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2.3.12 Figures

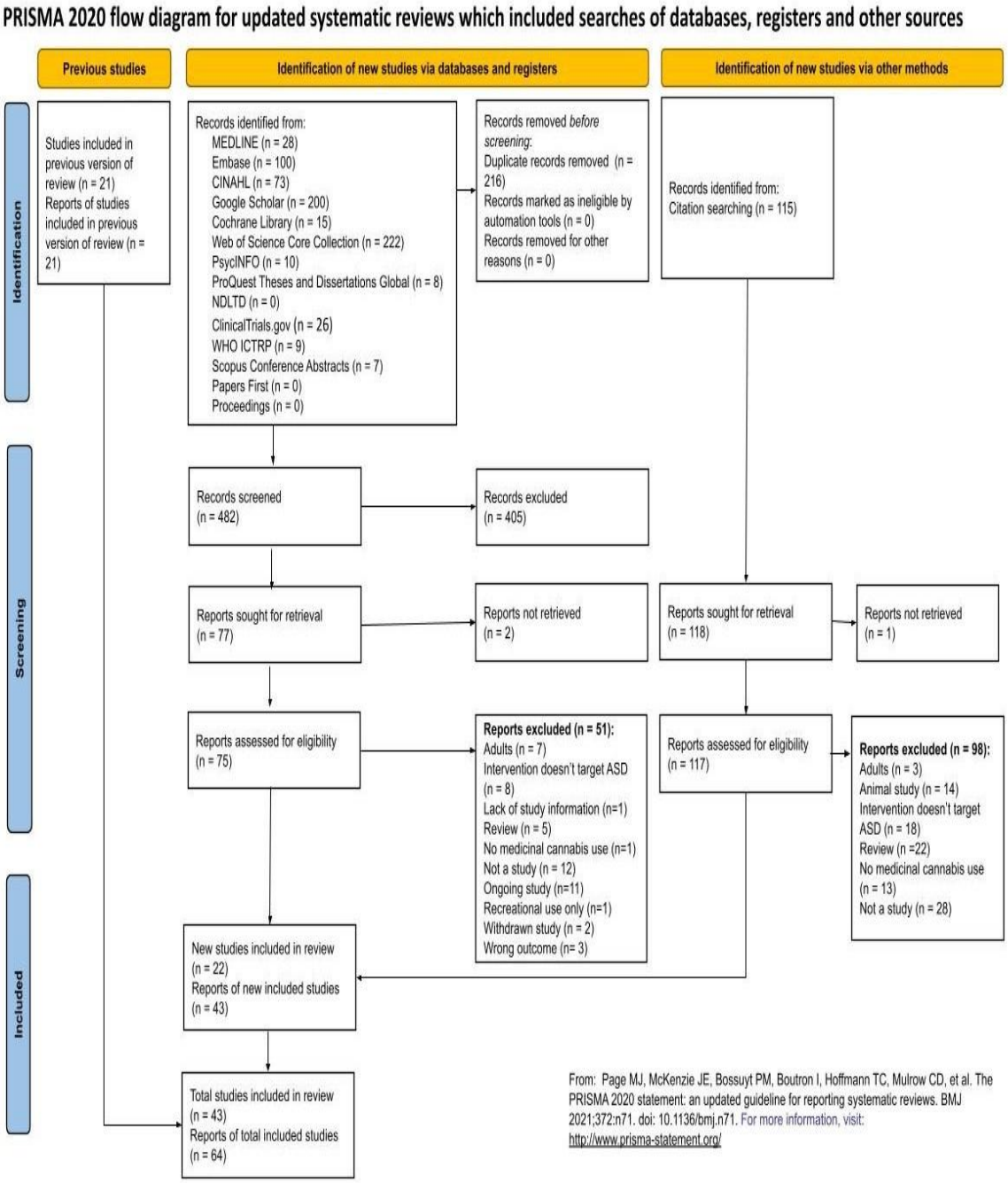


Figure 2.3.1. The PRISMA flow diagram of the included studies.

2.3.13 Tables

Table 2.3.1. Characteristics of the included studies and participants.

Author, Clinical trial registry	Study design	Study centers, location	Sample size % female/male, No %	Age of subjects using cannabis, population, % with ASD	Duration	ASD diagnostic criteria	Co-morbidities
Case reports and case series							
Gaillard 2019(15)	Case report	Single center, US	1, 0/1(100)	7 years, Children, 100%	2 years of treatment	DSM-5	N/A
Kurz 2010(41)	Case report	Single center, Austria	1, 0/1(100)	6 years, children, 100%	6 months	DSM-IV / early infant autism (F84.0)	N/A
Ma 2022 (42)	Case report	Single center, Canada	1, 0/1(100)	9 years, children, 100%	NR	N/A	Type 1 diabetes mellitus and asthma
Nogueira 2023(43)	Case report	Single center, Brazil	1, 0/1(100)	21 years old (took medical cannabis when he was a child), adult who used medical cannabis as a child, 100%	N/A	N/A	N/A
Nunes 2023(44)	Case report	Single center, Brazil	1, 0/1(100)	12 years, children, 100%	N/A	DSM-5	Epilepsy
Ponton 2020(45)	Case report	Single center, Canada	1, 0/1(100)	15 years, children, 100%	N/A	Diagnosed by Interior Health Children's Assessment Network	Overweight, epilepsy, anxiety, insomnia
Raz 2022(46)	Case report	Single center, Italy	1, 0(0)/1(100)	17 years, children, 100%	N/A	N/A	N/A
Al-Soleiti 2022(47)	Case series	Single center, USA	3, 0(0)/3(100)	22 ± 1.41 (20-23) years, at age of 16 started CBD treatment, adults who used cannabis	N/A	DSM-5	Epilepsy, GERD, depression, mania

				during adolescence, 100%			
Anderson 2022(49)	Case series	Single center, Australia	2, 0/2(100)	29 ± 12 (17-41) years, Child, and adult, 100%	N/A	N/A	ADHD, OCD, hay fever, seizures, iron deficiency
de Souza Mazza 2022(48)	Case series	Single center, Brazil	15, 2 (13.3)/13(86 .7)	11.1 years, children, 100%	6 months	N/A	N/A
Cross-sectional surveys and qualitative studies							
David 2024(55)	Cross-sectional survey and qualitative (mixed methods)	Single center, Israel	Survey 87, qualitative 15, 71(81.6)/16 (18.4)	7.39 ± 2.02, Children, 10%	6 months	ADOS-2	N/A
DiLiberto 2022(16)	Cross-sectional survey	Multicentric, USA	89, 18 (20.2)/71(79 .8)	mean 9.9 (3.5, 19.0) years, children, and adults, 100%	N/A	ASD diagnosis from a qualified medical or mental health provider	N/A
Fossi 2023(52)	Cross-sectional survey	Single center, USA	50, N/A	NR, Parents of children with autism, 100%	N/A	N/A	N/A
Garcia-Romeu 2022(53)	Cross-sectional survey	Online survey, USA	1276 (cannabis users 808 and controls 468), 472(37)/804 (63)	Parents aged 38 ± 20 years Range 1-86 years, <18 years: (178) 22%, children and adults, N/A	Survey opens between April 2016 and Feb 2018	N/A	N/A
Krauss 2022(54)	Cross-sectional survey	Multicentric, USA	528, N/A	range 7-18 years, children, N/A	NA	N/A	N/A

Schwaller 2023(13)	Cross-sectional survey	Single center, USA	518, N/A	11.9 ± 3.79 (8–15) years, parents of children with anxiety and neurodevelopmental disorders including autism, N/A	N/A	N/A	OCS, GAD, ADHD
Sivori 2023(14)	Cross-sectional survey	Single center, USA	454, N/A	5-10 years, parents of children aged 5-10 years with autism, 100%	N/A	N/A	N/A
Lane 2022(12)	Qualitative interview	Not reported, USA	21 parents of children with autism, 3(14.3)/18 (85.7)	Parents 38.5 (27-52) years, children 8.3 1(8 months - 10 years) years, Parents of children with autism < 18 years, 100%	NR	N/A	N/A
Shaw 2023(56)	Qualitative ethnographic interviews	Single center, Canada	14 (parents 7 and health care professionals 7), 4(29)/10(71)	Parent 44.4 (7-32), children 15.7 (8-32) years, parents, and health professionals of 6 children and 1 adult, 57%	N/A	N/A	N/A
			Observational studies				
Aran 2019(57)	Retrospective feasibility study	Single center, Israel	60, 10 (17)/50(73)	11.8± 3.5 years (range: 5-17.5 years), children, 100%	7-13 months of treatment, mean treatment length was 10.9 ± 2.3 months	DSM-5	Epilepsy 14/60 genetic disorder 7/60, Prematurity 3/60, motor disability 3/60
Barchel 2019(59)	Prospective observational study	Single center, Israel	53, 8(15) 45 (85)	median: 11 (4-22) years, children, and adults, 100%	30 days of treatment minimum; median duration treatment was 66 days	DSM-4 or DSM 5	Hyperactivity symptoms 47/53, sleep problems 29/53, self-injury 47/53, social communication and reciprocity (n=22/53, anxiety 26/53

					(30-588 days range)		
Bar-Lev Schleider 2019(58)	Retrospective observational study	Multi centric, Israel	188, 34(18)/154(82)	12.9 ± (7.0) years, children, 100%	6 months	In accordance with the accepted practice in Israel	Epilepsy 27/188, ADHD 7/188, Tourette 4/188, celiac 3/188, anxiety disorder 3/188
Bilge 2021(60)	Prospective observational study	Single center, Türkiye	33, 6(18)/ 27(82)	7.7 ± 5.5 years, children, 100%	Average duration of treatment was 6.5 months (3-28 months); Median follow-up 4.6±1.3 years	DSM-5	Epilepsy 3/33
Fleury-Teixeira 2019(61)	Observational Study	Single center, Brazil	18, but 3 stopped treatment in first month,5 (28)/13(72)	mean 10 (6-17) years, children, 100%	6-9 months of treatment	ICD 10 = F84	Epilepsy 5/15
Kuester 2017(50)	Retrospective chart review	Single center, Chile	21, 6(29)/15(71)	mean age 9 years 10 months; range 26 month - 22 years, children and 1 adult, 100%	7.6 Months (3-12 months)	DMS-5	N/A
Liz 2022(62)	Prospective observational study	Single center, Brazil	27, N/A	mean 7.2 ± 2.9 years, children, 100%	24 weeks	N/A	Avoidant Restrictive Food Intake Disorder, ADHD, insomnia disorder, but not all reported
McVige 2020(51)	Retrospective chart review	Single center, US	20, N/A	NR, children, 100%	NR	N/A	Epilepsy 6/20, pain 14/20
Montagner 2023(63)	Retrospective observational study	Single center, Brazil	20, 2(10)/18(90)	14 (5-38) years, children, and adults, 100%	Minimum of 6 months	ICD 10=F84.0	N/A

Nazareno 2023(64)	Retrospective open label study	Not reported, US	113, N/A	3-17 years, children, 100%	3-24 months	N/A	N/A
Zürcher 2022(65)	Retrospective observational study	Single center, Switzerland	90 (CBD 51 and THC 39), 32(36)/58(64)	Median: 11.5 (6–15) years, children, 8%	study duration February 2008 and June 2019	N/A	Drug-resistant epilepsy, Dravet syndrome, Lennox–gastaut syndrome, cerebral palsy, Encephalopathy, metabolic disease, genetic disorder, cancer, Tourette's syndrome, severe head injury
Interventional studies							
David 2024(71)	Open-label study	Single center, Israel	65, 12(18.5)/53(81.5)	mean ± SD 7.39 ± 20.2, children, 100%	6 months of treatment	ADOS-2	N/A
Hacohen 2022(17)	Non-randomized, single arm open-label trial	Single center, Israel	82, 34(41)/48(59)	mean 9.2 (5-25) years, children, and adults, 100%	6 months of treatment	DSM-5	Sleep problems, irritability/aggressive behaviour, hyperactivity and attention deficit disorder, anxiety
Kruger 2006(69)	Non-randomized open-label trial	Single center, USA	10, 2(20)/8(80)	mean ± SD 14.4 ± 1.91; 14 (11-17) years, children, 40%	6 months	N/A	Angelman Syndrome, aggression, fragile x syndrome, aphasia, visual impairment, PDD-NOS
Castellanos 2022, NCT03900923(66)	Open Phase 2 Trial	Single center, USA	19, 1(5.2)/18(94.6)	11.3 ± 2.9 (7-17) years, children, 100%	6 weeks	ADOS-2 and DSM-5	ADHD–Combined 12/19, ADHD–Inattentive 4/19, OCD 4/19, Anxiety 3/19, and Other–Specified disruptive and impulse control disorder 2/19
Heussler 2022(68)	Non-randomized open-label study	Single center, Australia	37, N/A	mean 9.2 years (3-17) years, Children, 100%	38 weeks treatment	DSM-5	N/A

El-Sukkari 2023, ACTRN12621000760875(67)	Open Label Study	Single center, Australia	18 enrolled, but 14 completed trial, 17 started treatment, 6(35.7)/12(64.3)	mean 13.4 (10-17) years, Children, 100%	4 weeks of treatment	DSM-5 confirmed by ADOS-2	NA
Scheffer 202(70)	Non-randomized controlled trial	Multicentric, Australia and New Zealand	48, 22(45.8)/26(54.2)	mean 10.5 ± 3.8 years, Children, 29%	6.5 months of treatment	N/A	Dravet syndrome 8/48, Lennox-gastaut syndrome 5/48, myoclonic-atonic epilepsy 6/48, west syndrome 3/48
Stolar 2022, NCT05212493(18)	Non-randomized open-label study	Single center, Israel	59, 9(15.3)/50(84.7)	mean 10 ± 4.6 (5-25) years, Children and young adults, 100%	6 months of treatment	DSM-5	N/A
Parella 2024, ACTRN12622000437763(74)	Randomized cross-over trial	Single center, Australia	29, 11 (37.9/18(62.1)	mean 9.62± 2.05, Children and adult, 100%	24 week of treatment (12 week each group), and 8 weeks washout	ADOS-2	N/A

Abbreviations: ADOS Autism Diagnostic Observation Schedule, ADHD Attention deficit hyperactivity disorder, CBD Cannabidiol, DSM: Diagnostic and statistical manual, GAD Generalized anxiety, GERD: Gastroesophageal reflux disease, ICD International classification of diseases disorder, N/A Not available, OCD Obsessive–compulsive disorder, PDD-NOS Pervasive Developmental Disorder-Not Otherwise Specified, THC Tetrahydrocannabinol

Table 2.3.2. Primary Safety outcomes reported in the included observational and single-arm studies.

Safety outcomes	No. of studies	Events/ total	I^2 (%)	Pooled proportion [95% CI]
AEs	9	327/1255	94	44.8% [24.1-67.4%]
AEs-cannabinoid				
Purified CBD	2	75/85	80	89.2% [57.8; 98.0%]
CBD-enriched CHE	3	60/163	85	41.1% [23.7- 61%]
Cannabis herbal extract, unspecified	1	3/20	0	15% [3.2-37.9%]
Dronabinol	1	25/90	0	27.8% [18.9-38.2%]
CBD-enriched CHE and Purified CBD	1	34/89	0	38.2% [28.1-49.1%]
Medical Cannabis, Unspecified	1	130/808	0	16.1% [13.6- 18.8%]
AEs-study design				
Non-randomized trials	2	75/85	80	89.2% [57.8-98%]
Observational studies	4	85/253	8	36.9% [24-52.1%]
Treatment chart review	1	3/20	0	15% [3.2-37.9%]
Cross-sectional survey	2	164/897	96	25.3% [9.7-51.6%]
Withdrawals	11	141/648	73	19.6% [13.7-27.3%]
Withdrawals-cannabinoid				
Purified CBD	1	8/48	0	16.7% [7.5-30.2%]
CBD-enriched CHE	7	88/482	56	17% [11.4-24.5%]
Dronabinol	2	42/100	46	36.2 [17.7-59.9%]
CBDA-enriched CHE	1	4/18	0	22.2% [6.4-47.6%]
Withdrawals-study design				
Non-randomized trials	4	42/186	0	22.8% [17.3-29.5%]
Observational studies	7	99/462	83	17.4% [9.6-29.5%]
Serious AEs	2	19/147	84	7.4% [0.6-50.9%]
Serious AEs-cannabinoid				
CBD-enriched CHE	1	1/57	0	1.8% [0-9.4%]
Dronabinol	1	18/90	0	20% [12.3-29.8%]
Serious AEs-study design				
Observational studies	2	19/147	84	7.4% [0.6-50.9%]
Withdrawals due to AEs	8	47/575	71	7.4% [3.9-13.4%]
Withdrawals due to AEs-cannabinoid				
Purified CBD	1	2/85	0	2.4% [0.6-9%]
CBD-enriched CHE	4	26/382	65	7.3% [3.6-14.1%]
Dronabinol	1	18/90	0	20% [12.3-29.8%]
CBDA-enriched CHE	1	1/18	0	5.6% [0.1-27.3%]

Withdrawals due to AEs-study design				
Non-randomized trials	4	15/213	34	5.9% [2.3-14.1%]
Observational studies	4	32/363	83	8.6% [3.4-20.1%]

2.3.14 Supplementary material

2.3.14.1 eTables

eTable 2.3.1. Characteristics of the included studies, cannabinoids, and reported benefits of cannabinoid use in children with ASD

Author	Study design	Cannabinoids, dose, route, frequency	Other drugs (when starting Cannabis)	Outcome scales	Reported benefits
			Case reports and case series		
Gaillard 2019(15)	Case report	CBD oil 9-60 mg/day, sublingual, oral, NR	N/A	ATEC	Within 2 weeks, less social anxiety and improved sleep was observed. After 3 months, increased focus and attention, compliance with instructions, work completion, transitioning between activities, peer interactions, a decrease in social anxiety and able to attend kindergarten without support.
Kurz 2010(41)	Case report	Dronabinol, 0.62-3.72 mg/day, oral, NR	N/A	ABC	Decrease in Hyperactivity by 27 points, lethargy by 25 points and irritability by 12 points, Stereotypic behaviour decreased by 7 points and inappropriate speech improved by 6 points
Ma 2022(42)	Case report	CBD oil (CBD 20mg, THC <1mg), 1-5 mg/kg/day, oral, NR	N/A	Self-injurious behaviours, inappropriate behaviours, communication difficulties, sleep problems, poor academic performance, time in sensory room at school, irregular eating pattern	Improvement in self-injurious behaviours, inappropriate behaviours, communication difficulties, sleep problems, poor academic performance, time in sensory room at school, irregular eating pattern, anxiety
Nogueira 2023(43)	Case report	CBD-enriched CHE (100%: 0.3% CBD: THC), 270 mg/day, Oral, NR	Fluoxetine and periciazine	Subjective reporting of outcomes	Improvement in autism symptoms, patient was more attentive, affectionate, less aggressive and organized
Nunes 2023(44)	Case report	CBDA-enriched CHE, (CBDA: THCA 2:1), CBDA: 1.5 mg/day, THCA: 0.6mg/day, oral, NR	Sodium valproate, aripiprazole, fluoxetine, topiramate, lamotrigine, periciazine,	Subjective reporting of outcomes	Improvements in clinical condition, stabilized and calmer behavior, reduction in episodes of agitation, resulting in normal school routine

			trazodone hycloridate		
Ponton 2020(45)	Case report	CBD-enriched CHE (20:1 CBD: THC), Dose range CBD 4-20 mg/day, THC: 0.2 to 1 mg/day	Lamotrigine, lorazepam, melatonin, riboflavin, ranitidine, magnesium	Subjective reporting of outcomes	Positive effect of CBD enriched CHE on behavioral symptoms, anxiety, sleep, as well as social deficits
Raz 2022(46)	Case report	CBD-enriched CHE, 21.6 mg/day, Terpene-enriched CHE terpenes/cannabinoids: 0.15/2.5, 11.2 mg/day, oral, NR	Perithiazine, aripiprazole, lorazepam	Subjective reporting of outcomes	Strong improvement in efficacy including reduction in aggression, and improvement in speech as well as sense of humor after replacing purified CBD oil with terpene-enriched CBD oil in child with ASD
Al-Soleiti 2022(47)	Case series	Patient 1 CBD enriched CHE (THC<0.3%), 10 drops, Oral, BD; Patient 2 and 3 Vaporized cannabis (20% THC and 10% THC), NR	Lacosamide, omeprazole, duloxetine, trazodone, buspirone, quetiapine, and melatonin	Subjective reporting of outcomes	Use of cannabis was associated with mania and psychosis
Anderson 2022(49)	Case series	CBD-enriched CHE (>98% CBD) 18 mg/day to 25 mg/day, oral, BD and CBD 50 CHE (50 mg CBD/ml and <0.2 mg THC/ml), 12.5 mg, Oral, BD	Clonidine, loratadine, fluoxetine, and risperidone	Subjective reporting of outcomes	Patient 1 (<18 years): No therapeutic benefit found after 2 weeks, instead parents reported insomnia, increased agitation, hyperactivity, vocal yelling, worsening OCD, CBD was discontinued, and adverse events resolved; after dose increased, more improvement in communication, sleep, anxiety, and reduction in panic attacks
de Souza Mazza 2022(49)	Case series	CBD and THC solution (100:1 CBD: THC), 1-5 mg/kg/day, oral, NR	N/A	Aggressiveness, social cognition, learning capabilities, language, sleep, appetite, and collateral effects, through clinical evaluation, neuropsychological	12 showed improvement in social cognition, 10 had less aggressiveness, 10 presented a higher degree of interest in communication and language usage, 7 demonstrated better learning capabilities

				testing, and questionnaire answered by the parents	
Cross-sectional surveys and qualitative studies					
David 2024(55)	Cross-sectional survey and qualitative (mixed methods)	CBD-enriched CHE, maximum CBD 10mg/k/day (400 mg/day), THC 0.5mg/kg/day (20 mg/day)	N/A	Factors influencing adherence and drop out rates of medical cannabis treatment	Symptoms target with CBD-enriched CHE were repetitive and restrictive behaviours, communication skills, Aggression, self-aggression, and tantrums, daily activities Common reasons for dropout were lack of efficacy (n=9), side effects worsen functioning (n=2), violence (n=3), weight gain (n=1), sleep problem (n=1), major reported barrier was unrealistic parents expective
DiLiberto 2022(16)	Cross-sectional survey	CBD-enriched CHE, purified CBD, oral, NR	Supplements 45/89, anti-convulsant 10/89, antihistamine 19/89, anti-adrenergic agent 18/89, anti-psychotic 13/89, anti-depressant 17/89, bronchodilator 2/89, proton pump inhibitor 7/89, antibiotic 5/89, NSAIDs 3/89, mucolytics 2/89, CNS stimulant 4/89, GI support 3/89, anxiolytic 4/89	ASD behaviours, ADHD behaviours, anxiety, irritability, sleep on a 1-10 scale	Caregivers rated cannabis rating: moderately effective in treating behaviours of interest in children with ASD. Increased CBD dose improved effectiveness of ASD irritability and behaviours with low THC
Fossi 2023(52)	Cross-sectional survey	Medical cannabis, unspecified, oral, NR	N/A	Change in symptoms: aggression, irritability, meltdowns, Anxiety, OCD, focus/ADHD, communication, GI issues, insomnia, self-Stim behaviour, hyperactivity, pain, appetite, rage, agitation, self-injury	Common symptom treated with medical cannabis, irritability n=24, improvement aggression, irritability, meltdowns, anxiety, agitation, and communication reported by 40% of participants

Garcia-Romeu 2022(53)	Cross-sectional survey	Variety of products including CBD-containing products, THC, cannabis flowers, cannabis-based oils, edible cannabis products, Vape pens, tetrahydrocannabinolic acid, and transdermal products, NR	N/A	Qualitative thematic analysis, World Health Organization quality-of-life assessment, numeric pain rating scale, hospital anxiety and depression scale, Pittsburgh Sleep quality Index for adults, CSHQ-A for children	624/808 (77%) reported benefits of cannabis use (improvement in physical symptoms 446/808, mental health (quality of life 116/808, reduced medication or health care utilization 93/808), Cannabis users reported better quality of life, greater health satisfaction, improved sleep and lower average pain severity, lower anxiety and lower depression when compared with controls
Krauss 2022(54)	Cross-sectional survey	CBD products, unspecified, oral, NR	N/A	Subjective reporting of outcomes	30.9% (n=162) of parent reported using CBD products in children with ADHD, GAD, and/or ASD
Schwaller 2023(13)	Cross-sectional survey	Unlicensed CBD products, Unspecified, oral, NR	N/A	Quantification of unlicensed CBD products among pediatric patients diagnosed with anxiety and neurodevelopmental disorders and compare the perceptions of CBD between parents who administer and who do not administer CBD products to children	Parents would prefer to administer CBD (unlicensed) in children with GAD only (36.1%) compared with ADHD only (25.2%) and ASD only (27.7%), and common unlicensed CBD products were chewable gummies 56/518, oils 9/518, drops 7/518, tinctures 6/518, lotions or creams 4/518, and lollipops or edibles 3/518
Sivori 2023(14)	Cross-sectional survey	Medical cannabis, unspecified, oral, NR	Anticonvulsant, antihypertensive, antipsychotic, benzodiazepine, CNS stimulant, Endogenous hormone, peptide hormone, selective norepinephrine uptake inhibitors, selective	Caregiver's experience, knowledge and interest in medical cannabis use for children with autism	Familiarity of cannabis use in children with ASD 41/454, willing to try cannabis for children 347/454, and internet as source of information 211/454, common symptoms to target: difficulty focusing, eating problems, hyperactivity, sensory sensitivities, anxiety, and unusual fears or obsessions, and challenges attending to tasks

			serotonin reuptake inhibitors,		
Lane 2022(12)	Qualitative Interview	Medical cannabis, unspecified, oral, NR	N/A	Parent perspectives regarding cannabis use for children with ASD as well as potential symptom targets	Limited knowledge about cannabis uses in children with ASD, while common source of information were Internet and social media
Shaw 2023(56)	Qualitative ethnographic interviews	Purified CBD, CBD enriched CHE (15:0.7, 1:20 CBD: THC), oral, NR	N/A	Policy barriers for parents of neuro-diverse children and their health care supporters in accessing cannabidiol as a treatment in British Columbia, Canada	Six common barriers in accessing CBD as treatment were ‘‘Costs associated with cannabidiol treatments’’, ‘‘Education on the subject and going through their networks to self-educate’’, ‘‘Lack of research and medical studies’’, and ‘‘Adverse events and risks associated with first-line pharmaceutical treatments”
			Observational studies		
Aran 2019(57)	Retrospective feasibility study	CBD-enriched CHE (20:1), 1 mg/kg/day to 10 mg/kg/day, sublingual, BD, or TDS	Antipsychotics 43/60, mood stabilizers 10/60, benzodiazepines 7/60, SSRIs 4/60, stimulants 4/60	A modified Liverpool adverse events profile, CGI-C, HSQ-ASD and APSI	CGI-caregiver (CGI-I ≤ 2) - 37/60, Improvement in anxiety in 23/60 of children and improvement in communication problems in 28/60, mean improvement in HSQ-ASD was 1.38 ± 1.79 (median = 0.81), and mean improvement in APSI 0.66 ± 0.74 (median = 0.53)
Barchel 2019(59)	Prospective observational study	CBD-enriched CHE (20:1), CBD 16mg/kg (maximum dose 600 mg/day) and THC 0.8mg/kg (maximum dose 40 mg/day), oral, NR	Stimulants 5/53, typical antipsychotics 6/53, atypical antipsychotics 31/53, anti-epileptic 8/53, melatonin 4/53, anti-depressant 2/53, other anti-muscarinic 3/53, alpha agonist 1/53	Parents reported on improvement in the co-morbid symptoms	Overall improvement 38/51, improvement in hyperactivity symptoms 26/38, self-injury 23/34, sleep problems 15/21, anxiety 8/17
Bar-Lev Schleider 2019(58)	Retrospective observational study	CBD-enriched CHE (30% CBD and 1.5% THC) and, mean CBD dose 79.5 ± 61.5 mg, mean THC dose 4.0 ± 3.0 mg and 5.0 ±	Antipsychotics 55/188, antiepileptics 46/188, antidepressants n=10/188, hypnotics, and	Quality of life, symptoms (restlessness, rage attacks, agitation, sleep problems, speech impairment, cognitive impairment, anxiety, incontinence, seizures, limited mobility,	Significant improvement in symptom 28/93, moderate improvement 50/93, slight improvement 6/93, no change 8/93, good quality of life rating before vs after treatment 31.3% vs 66.8%, good mood before vs after treatment 42% vs 63.5%, ability to dress and shower independently before and after treatment 26.4% 42.9%, good sleep before 3.3% vs and after treatment and good concentration before and after treatment 0% vs 14%

		4.5 mg THC/day (3% THC), oral, TDS,	sedatives 10/188, anxiolytics 7/188	constipation, tics, digestion problems, increased appetite, depression), medications used. primary outcomes: safety (adverse events), autism severity assessment, patient reported global assessment approach	
Bilge 2021(60)	Prospecti ve observati onal study	CBD-enriched CHE, mean CBD dose 0.7 mg/kg (range 0.3–2 mg/kg), maximum CBD 40 mg/day dose sublingual, BD, or TD	Oxcarbazepine, valproic acid, risperidone, aripiprazole	Parents assessed overall effectiveness, specifically looking at behavioural problems, expressive language, cognition, social interaction, stereotypes	No change in daily life activity in 6/33 patients, decrease in behavioural problems 10/33; increase in expressive language 7/33, improved cognition 4/33, increase in social interaction 3/33, decrease in stereotypes 1/33)
Fleury-Teixeira 2019(61)	Observat ional Study	CBD THC capsules (75:1 CBD: THC), mean CBD dose 2.90 mg/kg/day, range 2.30- 3.60 mg/kg/day, mean THC dose 0.06 mg/kg/day, range 0.05-0.09 mg/kg/day, oral, BD	Risperidone, oxcarbazepine, levomepromazine, carbamazepine, valproate, topiramate, lamotrigine, levomepromazine	Parent/patient reported improvement in attention deficit/hyperactivity disorder, behavioral disorders, motor deficits, autonomy deficits, communication and social interaction deficits, cognitive deficits, sleep disorders, seizures	Patient reported median improvement in seizures >50%: 5/5, behaviour disorder 20%, motor deficits 20%, autonomy deficits 10%, ADHD 30%, sleep disorders, communication, and social Interaction deficits 25%, sleep deficits 40%, and cognitive deficits 20%
Kuester 2017(50)	Retrospe ctive chart review	Balanced CBD THC product, high CBD, and High THC, oral, NR	N/A	CGI-I, APSI, core symptoms of ASD including social communication, language, repetitive behaviours, sensory difficulties, food acceptance, feeding and sleep disorders, seizures.	Significant improvement in CGI-I and APSI scores 66.7% of patients Most patients improved at least one of the core symptoms including social communication, language, and repetitive behaviours
Liz 2022(62)	Prospecti ve observati	CBD-enriched CHE, CBD 18.8mg/day, THC	N/A	Core ASD symptoms: communication, sociability, stereotypes behaviours;	Significant improvement in all core ASD symptoms: communication, sociability, stereotype behaviours. ($p<0.001$), improvement in avoidant restrictive food intake disorder, ADHD, Insomnia

	onal study	1.3 mg/day, oral, NR		neuropsychiatric comorbidity: avoidant restrictive food intake Disorder, ADHD, insomnia	
McVige 2020(51)	Retrospe ctive chart review	Medical cannabis, unspecified, oral, NR	N/A	CGI-C Scale measuring: QOL, activity limitations, symptoms, mood. A 10-point Likert scale measured: chronic pain change, epilepsy change; secondary efficacies	Improvement in seizure frequency (p =0.0032) and severity (p=0.0332), overall pain (p<0.0001), CGI-caregiver scale improvement in all areas (p<0.0001): quality of life, activity limitations, symptoms, and mood, improvement in sleep (p<0.0001), mood (p<0.0001), and aggression towards self-and/or others (p<0.0001), patient communication abilities (p=0.0001) and attention/concentration (p=0.0002)
Montagn er 2023(63)	Retrospe ctive observati onal study	CBD-enriched CHE (5.71 :3.07 CBD: THC), mean CBD dose range 46.63± 23.19 to 72.50 ± 37.82, THC dose range 7.09±7.42 to 12.68±12.31 mg/day, oral, NR	Risperidone, buspirone, methylphenidate, sertraline, aripiprazole, valproate, naltrexone, chlorpromazine, biperiden, belladonna, clonidine, risperidone, oxcarbazepine, clobazam, topiramate, periciazine, fluoxetine, levetiracetam, lamotrigine, lacosamide, quetiapine, bupropion	Attention deficit and hyperactivity disorder, abnormal behaviors, sadness, melancholy, bad moods, impaired motor development and motor coordination, lack of independence for daily activities, impaired communication and personal interactions (verbal and non-verbal), intellectual and cognitive deficits, sleep issues, seizures, avoidance and/or restrictions to food intake, positive mood states, overall patient's quality of life, adverse effects due to treatment, use of other medications, overall family's quality of life.	Improvement in percentage of patients', quality of life: 95%, family's quality of life: 83%, stereotypies: 80%, autistic meltdown crisis: 76%, discomfort in noisy places: 72%, aggressiveness toward others:67%, eating non-foods:63%, excessive appetite: 62%, obsessive-compulsive behaviors: 62%, self-aggressiveness:56%, screams and random sounds: 54%, improvement in attention to receptive direct verbal communication: 85%, visual contact and attention to conversation:75%, verbal communication: 50%, response to own name: 55%, written communication: 35.7%, alternative forms of communication: 58%
Nazareno 2023(64)	Retrospe ctive open label study	CBD: THC product, unspecified, oral, NR	N/A	Primary: changes in behavior, sleep, and quality of life assessed by CGI-C, Secondary: include dose-dependent effectiveness, tolerability,	CGI-C scores were improved for behavior, sleep, and quality of life

				and safety during the study period	
Zürcher 2022(65)	Retrospective observational study	Dronabinol, Medical cannabis tincture, oil, CBD products (2.5%, 5%, 10%), oral, NR	Antiepileptic drugs, muscle relaxants, analgesics, and opiates	Treatment success, side effects, and cost	59/90 caregiver reported successful cannabis treatment, participants treated with THC products reported a reduction of spasticity, pain, seizures, participants with CBD products reported reduction in seizures
				Interventional studies	
David 2024(71)	Open-label study	CBD-enriched CHE, maximum CBD dose 10 mg/kg/day (400 mg/day), THC 0.5 mg/kg/day (20 mg/day)	Sleep remedy treatment: 10/20, Stimulant drug: 6/20, antipsychotic drug: 4/20	Repetitive Behavior Scale-revised (RBS-R), Screen for Child Anxiety-Related Emotional Disorders (SCARED)	CBD-enriched CHE treatment was associated with improvement in SCARED subscale scores (general, separation, and social anxiety), RBS-R subscale scores, with differences in compulsive, ritual, and sameness between the three time points of data collection over 6 months. Interindividual variability of treatment responses was reported
Hacohen 2022(17)	Non-randomized, single arm open-label trial	CBD-enriched CHE, maximum CBD dose 10 mg/kg/day (400 mg/day), THC dose 0.5 mg/kg/day (20 mg/day), oral, NR	Melatonin: 14/110, aripiprazole: 9/110, risperidone: 7/110, coltiapine: 2/110, Periciazine: 2/110, quetiapine: 1/110, methylphenidate: 5/110, lisdexamfetamine: 4/110, atomoxetine: 2/110, dextroamphetamine: 1/110, guanfacine: 1/110, fluoxetine: 4/110, clonazepam: 2/110, dimethindene: 1/110	ADOS-2, Cognitive assessments: Wechsler Intelligence Scale; WPPSI, WISC or WAIS; Vineland adaptive behaviors scale, 3rd edition (Vineland-3), SRS-2	Significant changes in restricted and repetitive behaviour noted only by parent report and no significant changes in cognitive scores, mean change in in ADOS -0.56 ± 0.17 and Vineland scores 4.37±1.18 ($p<0.05$), CHSQ 4.37 ±1.18, mean change in ABC-I -0.56±0.17, SRS-2 -3.29 ± 1.13

Kruger 2006(69)	Non-randomized open-label trial	Dronabinol, 5- 20 mg/day, oral, QD	Naltrexone	Improvement in SIB	Significant improvement in self-injurious behaviour and mood/overall well-being 7/10
Castellanos 2022, NCT03900923(66)	Open Phase 2 Trial	Purified CBD, 3 to 9 mg/kg/day, oral, NR	N/A	Primary: CGI-I, RBS-R, SRS-2, School-Age Form Score, ABC - Irritability Subscale Score, ABC - Social Withdrawal Subscale Score, ADAMS, SCARED-Parent Version Score, SDSC, VABS-third edition (Vineland-3), Parent/Caregiver Form, CGI-S, AFEQ, ASC-ASD-P, ASC-ASD-C - Child Version, OSU Autism Clinical Global Impressions, BIS, HSQ-ASD, SWAN	Responders (CGI-I ≤ 2): 8/19, CGI–S scores (pre-CBD score vs post CBD scores): 4.68 ± 0.48 versus 3.95 ± 0.78
Heussler 2022(68)	Non-randomized open-label study	purified CBD gel, 500 mg/day, tropical, BD	N/A	ABC-C Irritability, PRAS-ASD, and APSI	Improvement in CGI-I (≤ 2): 77%, improvement in PRAS-ASD: 42%, APSI: 40%, and irritability ≥ 35%
El-Sukkari 2023(67)	Open Label Study	CBDV-enriched CHE, CBDA (62%), CBD (14%), CBGA (0.44%), CBDV (0.06%), and THC (0.08%), 5mg/kg/day to 20 mg/kg/day, mean 16.7 mg/kg/day (range 6-19 mg/kg/day), oral, NR	NA	Primary outcomes: Safety and tolerability (adverse events, complete blood count renal and liver function test); secondary outcomes: CGI-I for the Caregiver; CGI-I for the Clinician, CGI of Change in Target Behaviour; CGI-Change in Attention, CGI-Severity of Illness, ASC-ASD-P, ASC-ASD-C, SDSC	Improvement in CGI-S: 13/14, CGI-I (≤ 2): 8/14, Targeted behavioural problems rated as improved or very much improvement by 46% of treated patients. Total anxiety score reduced as reported by 62% of parents / 54% of children after 4 weeks, but 23% of parents and 36% of children reported increased anxiousness. Total sleep score decreased in the 11 children who were assessed, but not stat significant, Mean change in Anxiety scale: ASD-ASC-parent version: -4.4, ASD-ASC-children version -2.1; sleep disturbance scale: -2

Scheffer 2021(70)	Non-randomized controlled trial	Purified CBD gel, based on weight 25 kg or less 250- 750 mg, >25 kg 500 - 1000 mg/day, tropical, NR	Sodium valproate: 34/48, clobazam: 25/4, levetiracetam: 17/48, lamotrigine: 16/48, topiramate 12/48	Primary outcomes: safety (adverse events), change in seizures frequency	Median seizure reduction (IQR): 12.3% (−18.6% to 46.3%), median reduction in FIAS and TCS: 43.5% (−23.8% to 57.5%)
Stolar et al. 2022, NCT05212493(18)	Non-randomized open-label study	CBD-enriched CHE (20:1 CBD: THC) CBD 10mg/kg/day (max dose 400mg/day), THC 0.5 mg/kg/day, (max dose 20mg/day), oral, NR	Stimulants: 6/59, typical antipsychotics: 2/59, atypical antipsychotics: 6/59, anti-epileptics: 2/59, melatonin: 5/59, anti-depressant: 2/59, anti-muscarinic: 1/59, alpha agonist: 1:59	Biochemical analysis	No clinical or statistically significant differences were found for complete blood count before and after 3 months of CBD administration
Parella 2024, ACTRN12622000437763 (74)	Randomized cross-over trial	CBD-enriched CHE, CBD 5-10 mg/kg/day	Melatonin 9/29, non-stimulant 2/29, atypical antipsychotics 12/29, methylphenidate 10/29, SSRIs 10/29, SNRIs 2/29	SRS-2 scale, RBS-RM VABS-3, PedsQL, BRIEF 2, Personal wellbeing index school children, Developmental behaviour checklist-2, ASPI, PROMIS parent report-sleep health, social relationship, anxiety	Mean difference in SRS-2 score with CBD treatment compared to placebo -17 points (statistically non-significant), reduction in SRS-2 (CBD vs placebo) subscales awareness -2.6 vs 0.9, motivation -3.3 vs 0.8, cognition -2.8 vs -1.3, communication -5.1 vs -1.7, restricted repetitive behaviours -2.9 vs -2.1, PROMIS-social 1.7 vs -0.2, Vinland socialization subscale 4.4 vs 2.4, DBC2 social relating subscale -2.55 vs 0.29, PROMIS anxiety -4.1 vs 0.8, ABC score 2.4 vs 1, VABS-3 2.4, 1.3, APSI -5.7 vs -1.4
Aran 2021, NCT02956226 (72)	Proof-of-concept randomized double blind placebo controlled cross-over trial	CBD-enriched CHE and purified CBD (167mg CBD/ml, 8.35mg THC/ml), CBD 1 mg/kg/day to 10 mg/kg/day, THC 0.05 mg/kg/day to 0.5 mg/kg/day (maximum dose for	Any medication 108/150; antipsychotics: 81/150, SSRIs: 22/150, antiepileptic: 18/150, stimulant: 18/150, alpha-2 agonist 6/150	HSQ-ASD, CGI-C, SRS-2, APSI, LAEP, CSHQ, Experience and Expectations Checklist	Responders, CGI-I (≤ 2): Placebo: 10/47, CBD-enriched CHE: 22/45, Pure cannabinoids: 17/45. No significant difference in CSHQ total scores and subscale scores between cannabinoids and placebo. Median improvement in SRS-2 point (CBD-enriched CHE vs Pure Cannabinoids vs Placebo): 14.9 vs 8.2 vs 3.6 points, median change in HSQ-ASD: Placebo: −0.5 (−3.7 to 2.5) (n=39) , Pure cannabinoids −0.7 (−4.4 to 3.8) (n=42), CBD enriched CHE −1.1 (−3.8 to 1.6) (40); SRS-2 Placebo −3.6 (−63 to 35) (n=36), Pure cannabinoids −8.2 (−69 to 45) (n=28), CBD enriched CHE −14.9 (−45 to 15) (n=34);

		20–40 kg CBD 7.5 mg/ kg/day, THC 0.375 mg/kg/day, and > 40 kg CBD 420 mg CBD and 21 mg THC per day, oral, TDS			APSI: Placebo: −1.5 (−26 to 20) (n=42), Pure cannabinoids: −4.9 (−19 to 22) (n=42), CBD enriched CHE −5.4 (−39 to 13) (n=38)
da Silva 2022(20)	Randomized, double-blind, placebo-controlled	CBD-enriched CHE, (9:1 CBD: THC), CBD: 0.9-21 mg/day, THC: 0.1-1.75 mg/day, oral, NR	N/A	Semi structured interview prepared by authors related to ASD symptoms (aggressiveness, psychomotor agitation, concentration, no of meals/day, number of hours of sleep/day, social interaction with peers, verbal language, anxiety, and stereotyped movements; Autism Treatment Evaluation Checklist (ATEC), renal function test, liver function test, blood count and fasting glucose levels	Symptom outcomes (mean ± SD, cannabis versus control): aggressivity 1.39±1.36 vs 0.81±1.05; psychomotor agitation 2.65±1.14 vs 1.64±1.28; concentration 2.96±0.86 vs 1.71±1.07; meals 0.38±0.82 vs 1.32±1.90; sleep 0.28±0.59 vs 0.77±1.61; social interaction 2.83±1.10 vs 1.68±1.01; speech 1.72 ± 1.55 vs 1.32 ± 1.42; symptom outcomes (median ± SD, cannabis versus control) aggressivity 1.39±1.36 vs 0.81±1.05; psychomotor agitation 2.65±1.14 vs 1.64±1.28; concentration 2.96±0.86 vs 1.71±1.07; meals: 0.38±0.82 vs 1.32±1.90; sleep 0.28±0.59 vs 0.77±1.61; social interaction 2.83±1.10 vs 1.68±1.01; anxiety 2.90±1.23 vs 1.84±1.39; Stereotypy 2.07±1.03 vs 1.45±1.06
Efron 2021(19)	Randomised placebo-controlled trial	Purified CBD, 5 mg/kg/day to 20 mg/kg/day, maximum CBD dose for > 50 kg 1000 mg/day, oral, NR	Risperidone 3/8, fluoxetine 3/8, methylphenidate 1/8, clonidine 2/8, guanfacine: 1/8, sodium valproate:1/8, melatonin 2/8	ABC-I, Child & Adolescent Scale of Participation; Child Health Utility 9D; Sleep Disturbance Scale for Children; Assessment of Quality of Life 8D; Beach Center Family Quality of Life; Depression Anxiety Stress Scale - 21; APSI, Efficacy: Autism-Tics ADHD and Comorbidities, Social Communication Questionnaire, ABC, Depression Anxiety Stress	ABC-I reduction CBD: 12±2.1, placebo 2.5±0.4, CASP CBD: -14±-2.4, placebo -1.8± 3.4, CBD: APSI 8.6 ±1.9, Placebo: 4.5±1.6

				Scales, Child Health Utility 9D, QoL, Beach Family Quality of Life, SDSC, Safety: Monitoring of Side Effects Scale	
Oppenheim 2023(73)	Randomized placebo-controlled cross-over trial	Purified CBD, 5-20 mg/kg/day, oral, NR	N/A	Primary: Repetitive Behavior Scale-Revised, CBCL, ADOS- 2	Significant improvement in the motor skills subdomain in the CBD versus placebo group

Abbreviations ABC-I Aberrant behavior checklist- Investigator, ADAMS Autism diagnostic interview-revised, ADOS Autism diagnostic observation schedule, ATEC Autism treatment evaluation checklist, APSI Autism Parenting stress index, AFEQ Autism family experience questionnaire, CBC Child behavior checklist, CGI-C Clinical global impression-Caregiver, CGI-I Clinical global impression Investigator, CHSQ Children's sleep habit questionnaire, FIAS Frühintervention bei autistischen Störungen, LEAP Learning Experiences and Alternative Program, HSQ Home situations questionnaire, OCD Obsessive compulsive disorder, SDSC Sleep disturbance scale for children, SiB Self-injurious behavior, SWAN Strengths and weaknesses of ADHD-symptoms and normal-behaviors, SCARED Screen for children anxiety related emotional distress, TCS Therapist Confidence Scale VAB Vineland adaptive behavior scale, WPPSI Wechsler preschool and primary scale of intelligence, WISC Wechsler intelligence scale for children.

eTable 2.3.2. Cannabinoid-related adverse events reported by the included observational and single arm studies.

Safety outcomes	No. of studies	Events/ total	I^2 (%)	Pooled proportion [95% CI]
CNS-related AEs				
Aggression	2	11/199	0	5.6% [3.1-9.9%]
Agitation	4	13/858	93	7.4% [0.8-45.5%]
Anxiety	2	4/167	0	2.4% [0.9-6.3%]
Confusion	4	8/966	75	1.6% [0.4-6.1%]
Drowsiness	3	31/987	3	3.2% [2.2-4.5%]
Irritation	3	5/843	88	2.6% [0.2-24.3%]
Psychoactive effect	4	30/1078	90	3.8% [1.3-10.3%]
Restlessness	2	13/122	82	12.5% [3.4-36.5%]
Seizure	2	4/81	0	5.2% [2-13.1%]
Sleep disturbance	2	11/77	3	14.3% [8.1-24%]
Sleepiness	3	8/163	82	6.3% [1.1-29%]
Somnolence	2	18/101	42	17.8% [9.8-30.2%]
Respiratory system related AEs				
Cough	3	6/125	7	5.9% [2.7-12.5%]
GI system related AEs				
Constipation	3	3/162	0	2.2% [0.7-6.6%]
Decrease in appetite	6	22/287	16	9.0% [6-13.3%]
Dry mouth	3	9/238	0	4.1% [2.1-7.6%]
Gastrointestinal symptoms	2	7/148	3	5.1% [2.4-10.3%]
Increase in appetite	5	14/1024	77	2.9% [1-8.1%]
Nausea	3	10/951	77	1.7% [0.5-6.1%]
Eye-related AEs				
Eye redness	3	4/163	50	3.2% [0.8-12.4%]
General-AEs				
Fatigue	2	6/105	0	5.7% [2.6-12.2%]
Tiredness	2	16/102	83	22.7% [5.6-59.1%]
Weight gain	4	7/995	80	1.7% [0.3-8.6%]
Weight loss	2	5/77	64	7.7% [1.7-28.1%]
Urinary system-related AEs				
Urine incontinence	6	9/1039	76	2.4% [0.6-8.3%]

eTable 2.3.3. Cannabinoid-related adverse events reported by the included more than one RCTs.

Safety outcomes	No. of studies	Events/ total (%)		Risk Ratio	I^2 (%)	95% CI
		Cannabinoids	Control			
Serious AEs	1	5/188 (2.7)	1/94 (1.1)	NA	NA	NA
Withdrawals	2	16/205 (7.8)	7/111 (6.3)	1.45	29	0.44-4.81
Withdrawals due to AEs	2	2/205 (1)	1/111 (1)	1.50	0	0.22-10
Decrease in appetite	2	45/192 (23.4)	44/98 (44.9)	0.66	30	0.18-2.39
Decrease in weight	2	24/192 (12.5)	4/98 (4)	2.89	0	1.09-7.65

eTable 2.3.4. Cannabinoid-related adverse events reported by one RCT.

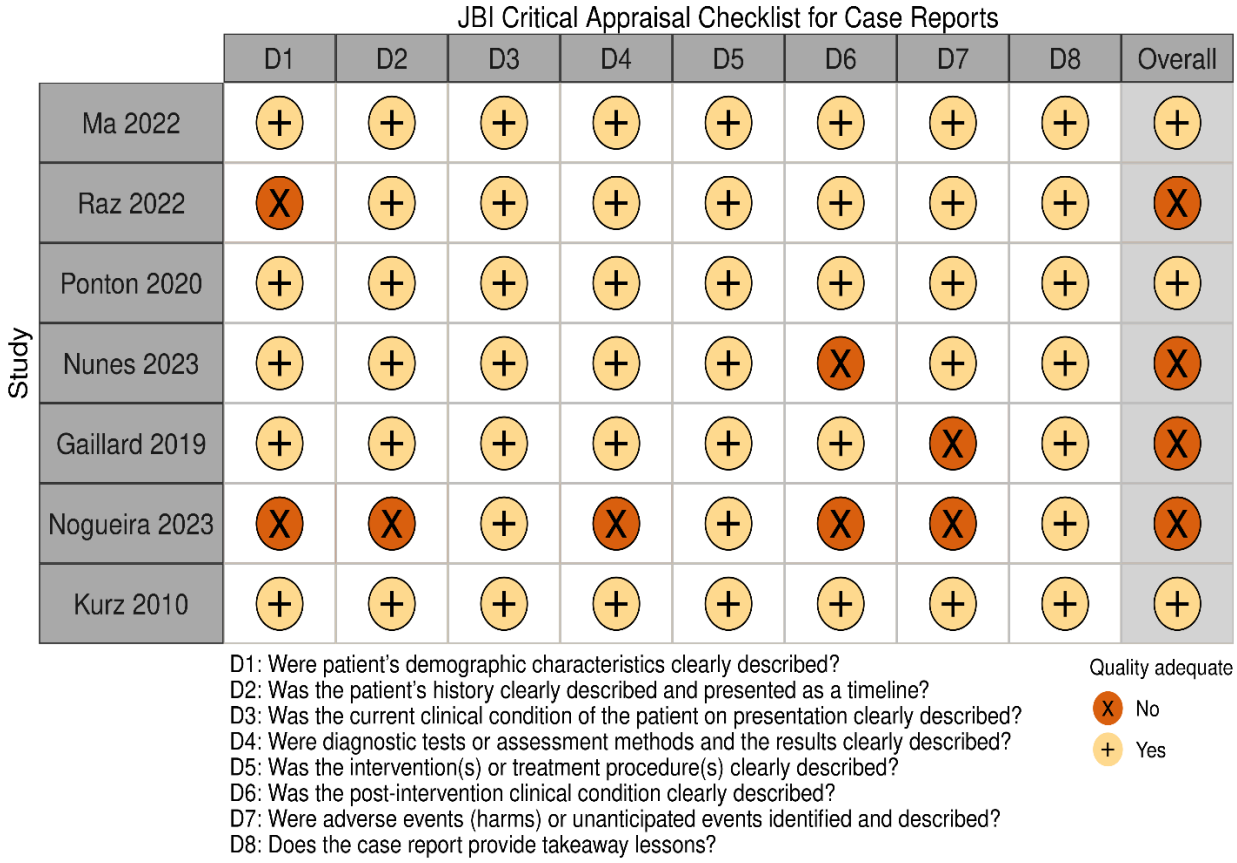
Author	Cannabinoid	Safety outcomes	Events/ total (%)	
			Cannabinoid	Control
Aran 2021	Cannabinoids	Overall AEs	168/188 (89.4)	78/94 (83)
Aran 2022	Cannabinoids	Somnolence	48/188 (25.5)	7/94 (7.4)
Aran 2024	Cannabinoids	Tiredness	56/188 (29.8)	18/94 (19.1)
Aran 2025	Cannabinoids	Euphoria	37/188 (9.7)	12/94 (12.8)
Aran 2026	Cannabinoids	Anxiety	44/188 (23.4)	13/94 (13.8)
Efron 2021	Purified CBD	Eyes rolled up	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Tics	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Ear ringing	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Headache	0/4 (0)	1/4 (25)
Efron 2021	Purified CBD	Drooling	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Abdominal pain	1/4 (25)	0/4 (0)
Parella 2024	CBD-enriched CHE	Abdominal discomfort	2/17 (11.8)	0/17 (0)
Efron 2021	Purified CBD	Increased appetite	1/4 (25)	1/4 (25)
Efron 2021	Purified CBD	Constipation	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Weight increased	1/4 (25)	3/4 (75)
Efron 2021	Purified CBD	Restlessness	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Nervousness	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Acne	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Crying	1/4 (25)	1/4 (25)
Efron 2021	Purified CBD	Urine incontinence	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Drowsiness	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Excessive sleep	1/4 (25)	0/4 (0)
Efron 2021	Purified CBD	Insomnia	1/4 (25)	1/4 (25)

eTable 2.3.5. Comprehensive description of ongoing studies related to cannabinoids in children with ASD.

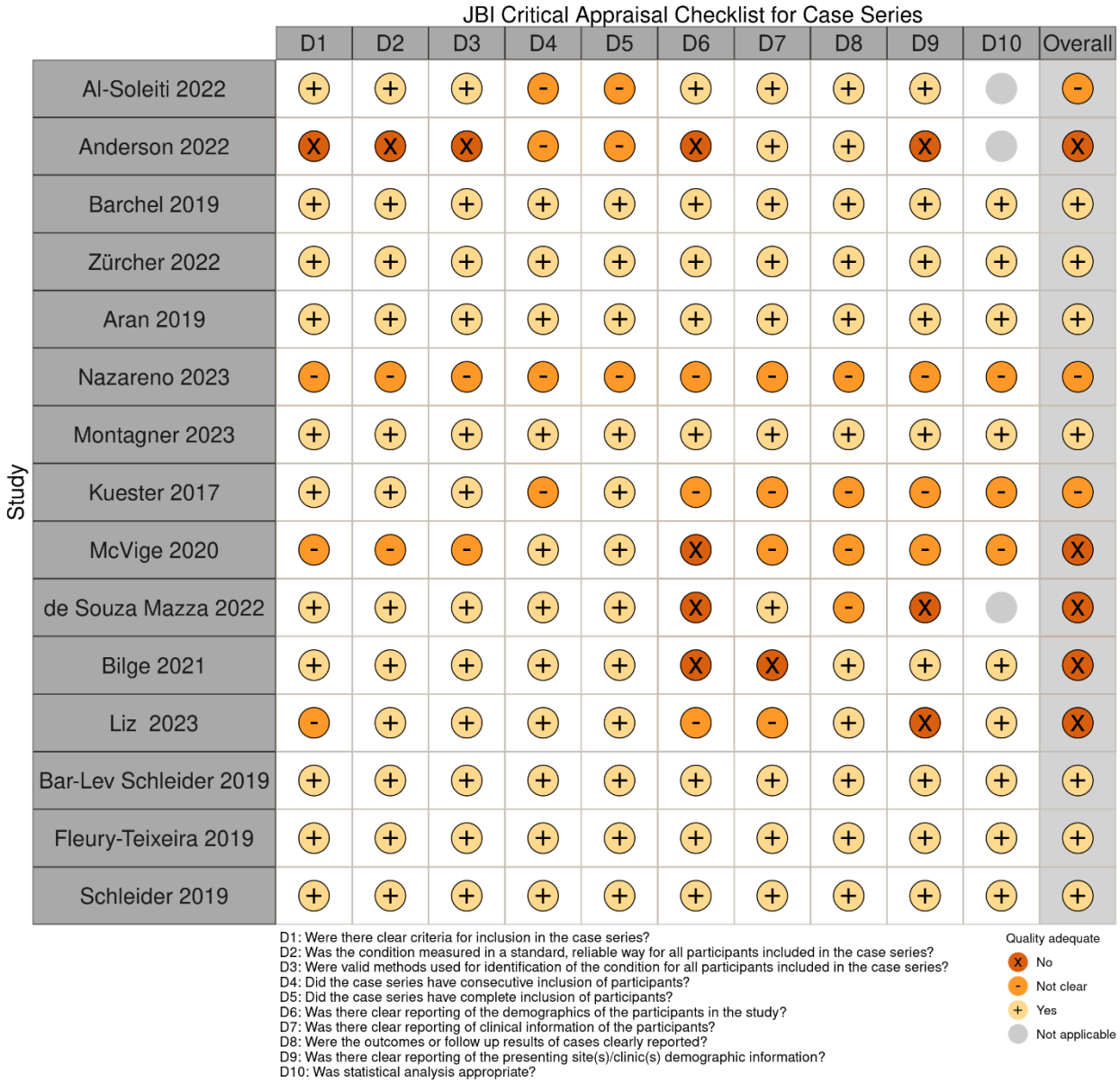
Registry name, number	Study design	Location	n	Cannabinoid, dose, frequency, duration	Control	Primary outcome	Study timeline
Clinicaltrials.gov, NCT03900923	Non-randomized controlled trial- single arm	USA	29	98% pure CBD, cohorts of size 3 receiving doses of 3, 6, or 9 mg/kg/day, 6 weeks	NA	Clinical global impression scale - improvement	March 12, 2019, to May 16 2024
Clinicaltrials.gov, NCT03202303	Randomized controlled trial	USA	100	Cannabidivarin	Placebo	Aberrant behavior checklist-irritability subscale	June 28, 2017, to July 2024
Clinicaltrial.gov, NCT04745026	Randomized controlled trial	Multicentric, USA, Australia, Canada, Germany, Spain, and UK	108	Purified CBD	Placebo	Aberrant behavior checklist subscale scores, vineland adaptive behavior scales-3 scores, clinical global impression improvement scores, change from baseline in clinical global impression severity scores	May 31, 2021, to December 21, 2023
Clinicaltrial.gov, NCT05516407	Phase 1 open label non-randomized controlled trial	Single centric, Australia	15	Full-spectrum medicinal cannabis plant extract, 0.08% THC	NA	Clinical global impression scale - improvement	April 1, 2021, to September 02, 2022
ANZCTR, ACTRN12621000370808	Observational study	Single centric, Australia	150	Oral oil formulations of cannabis, HOPE 1 and HOPE 2	NA	Aberrant behaviour checklist, clinical global impression, caregiver global impression of change, sleep disturbance scale, autism parenting stress index and	April 15, 2021, to June 06, 2022

						insomnia severity index - adults only	
Clinicaltrial.gov, NCT05626959, ANZCTR, ACTRN12622001398796	Randomized controlled trial	Single centric, Australia	54	Full-Spectrum Medicinal Cannabis Plant Extract with less than 0.08% THC (NTI164), 5-20 mg/kg/day	Placebo	Change in clinical global impression-severity	November 30, 2022 to November 30, 2023
Clinicaltrial.gov, NCT04520685	Randomized cross-over trial	Single centric, USA	70	CBD, 5-10 mg/kg/day	Placebo	Aberrant behavior checklist- 2nd edition irritability subscale raw score	December 15, 2021, to November 1, 2023
Clinicaltrial.gov, NCT03699527	Observational registry	Single centric, USA	119	Medical cannabis	NA	Number of children with ASD who use medical cannabis, maximum cannabinoid concentrations in pediatric patients with ASD	July 15, 2018, to January 15, 2020, no results posted
ANZCTR, ACTRN12621000760875	Phase 1/2 open label study	Single centric, Australia	20	Full-spectrum medicinal cannabis plant extract with 0.08% THC, 20 mg/kg/day	NA	Change in clinical global impression scale - improvement, change in vineland adaptive behaviour scales, safety as assessed by full blood examination	April 27, 2021 to August 26, 2022

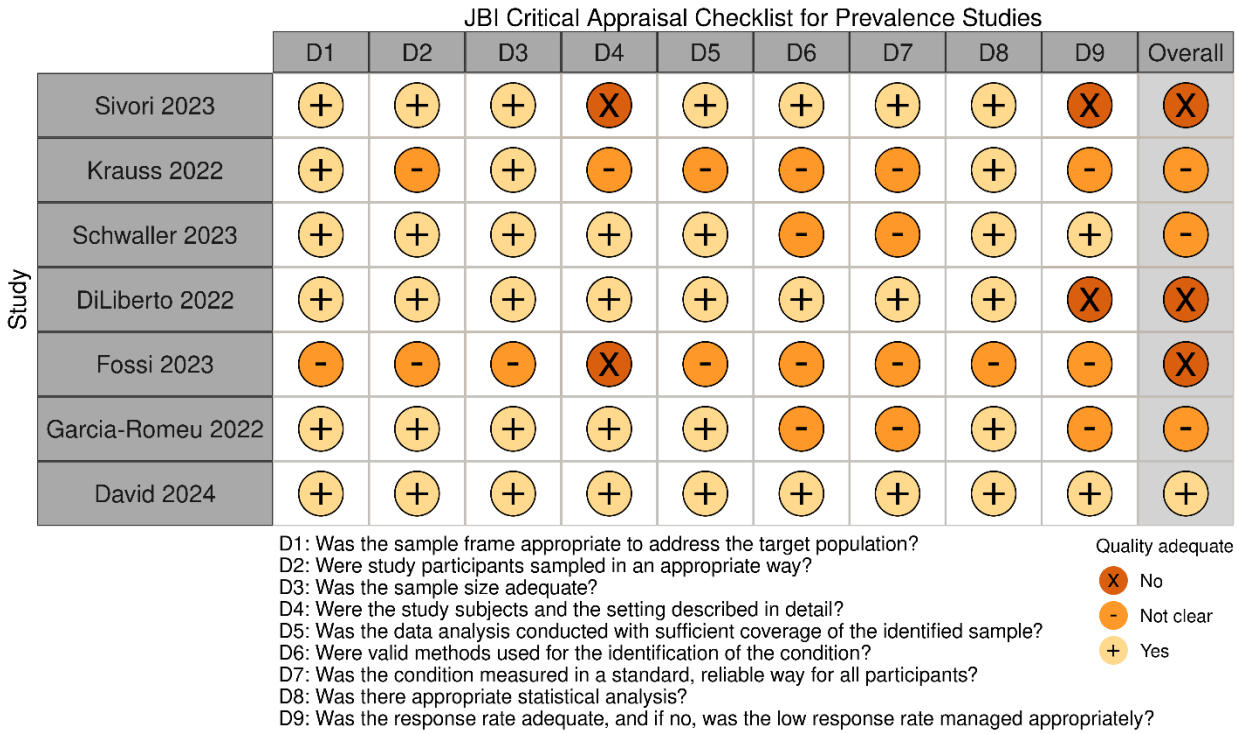
2.3.14.2 eFigures



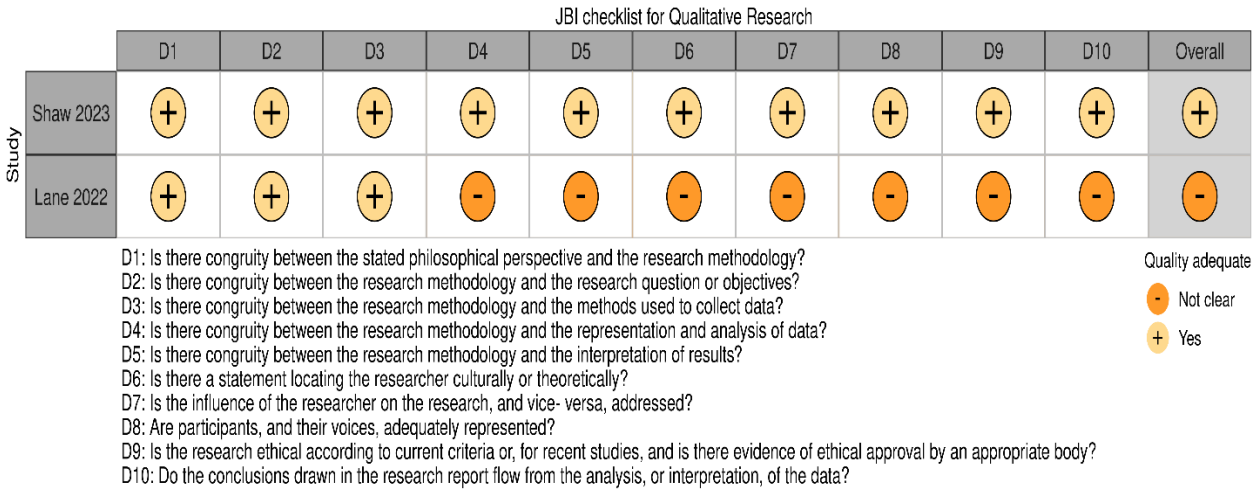
eFigure 2.3.1. Summary of the quality assessment of the included case reports.



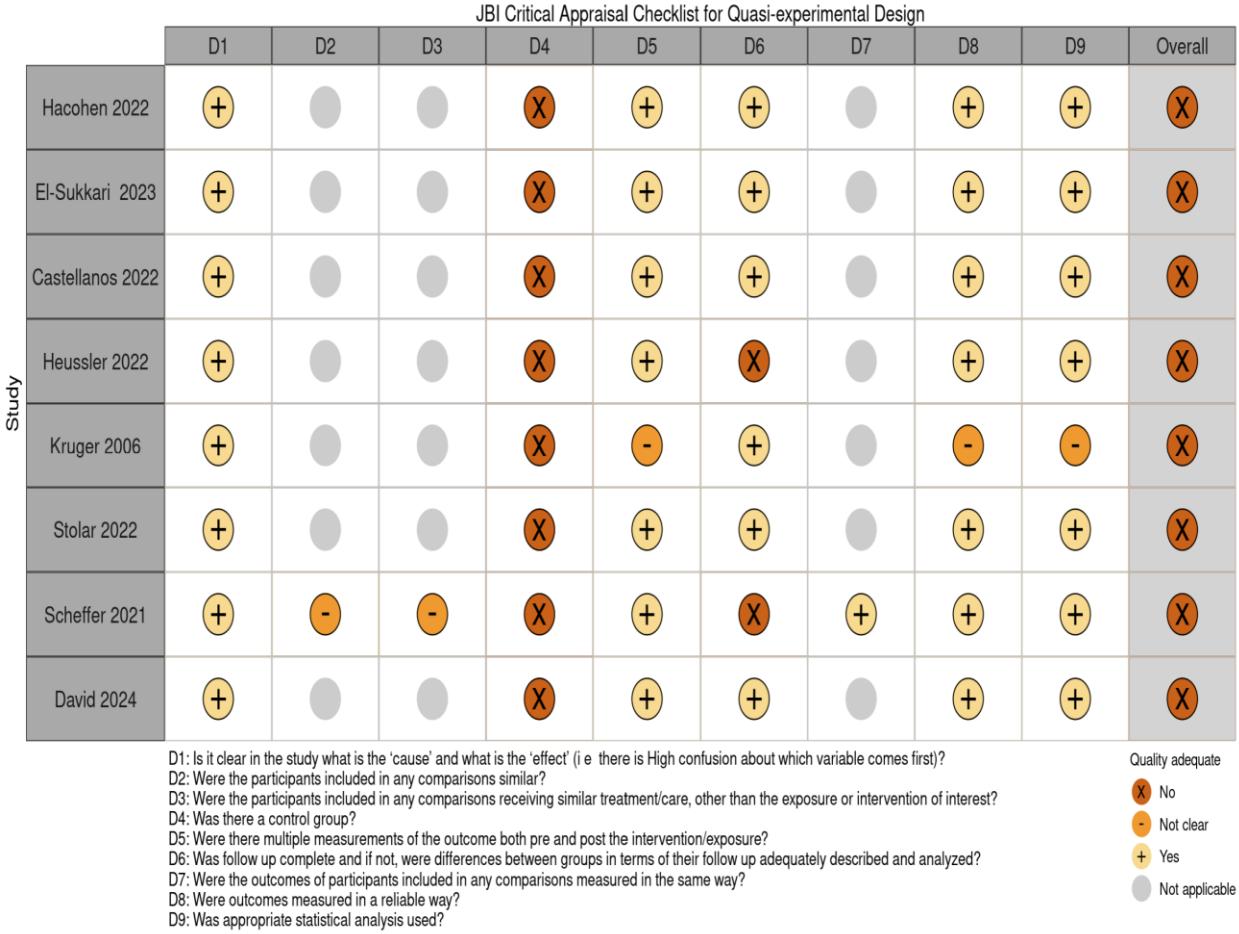
eFigure 2.3.2. Summary of the quality assessment of the included case series and treatment chart reviews.



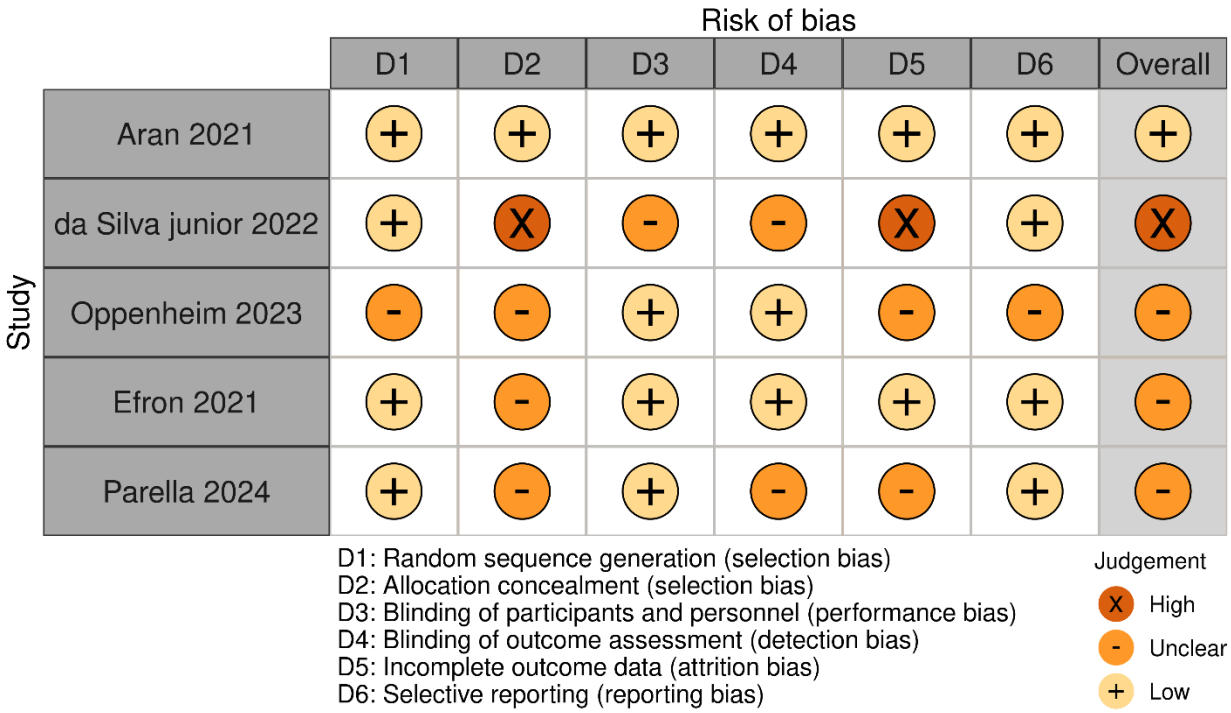
eFigure 2.3.3. Summary of the quality assessment of the included surveys.



eFigure 2.3.4. Summary of the quality assessment of the included qualitative interviews.



eFigure 2.3.5. Summary of the quality assessment of the included single-arm trials.



eFigure 2.3.6. Summary of the quality assessment of the included randomized controlled trials.

2.3.14.3 Search strategies

2.3.14.3.1 Ovid MEDLINE(R) ALL <1946 to January 17, 2024>

1 autism spectrum disorder/ or asperger syndrome/ or autistic disorder/ or child development disorders, pervasive/ 49345

2 (autis* or ASD or asperger* or PDD* or pervasive development* disorder* or childhood disintegrative disorder* or CDD or Heller* syndrome or disintegrative psychosis).tw,kf. 86940

3 1 or 2 90532

4 Cannabis/ 14491

5 exp Cannabinoids/ 18698

6 Cannabaceae/ 33

7 Medical Marijuana/ 2320

8 "marijuana use"/ or marijuana smoking/ 7112

9 cannab*.tw,kf. 49708

10 Mari#uana*.tw,kf. 17910

11 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla or CBD or indica or cannador).tw,kf. 26752

12 (19GBJ60SN5 or 2N4O9L084N or 7J8897W37S or K4H93P747O).rn. 10739

13 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9)tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex or methylcannabidiol or dimethylcannabidiol).tw,kf. 13887

14 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kf. 171

15 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kf. 6

16 or/4-1590119

17 3 and 16 312

18 exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or

elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. 5811134

19 17 and 18 148

20 exp Animals/ not (exp Animals/ and Humans/) 5187621

21 19 not 20 138

22 (2023* or 2024*).dt,ez,da. 1779896

23 21 and 22 28

2.3.14.3.2 Embase

https//access.ovid.com/custom/redirector/index.html?dest=https//go.openathens.net/redirector/ubc.ca?url=http//ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=1DSwiFqIqP1fnYDqDkYval90oK978LW5fgF86LGN2AXTmPXb38FzlESqNrD48H9XL

Embase <1974 to 2024 January 17>

1 autism/ or asperger syndrome/ or childhood disintegrative disorder/ or "pervasive developmental disorder not otherwise specified"/ 93140

2 (autis* or ASD or asperger* or PDD* or pervasive development disorder* or childhood disintegrative disorder*).tw,kf. 115925

3 1 or 2 132415

4 cannabis/ 45498

5 exp cannabinoid/ 89679

6 cannabaceae/ 163

7 exp "cannabis (genus)"/ 2084

8 medical cannabis/ 4261

9 exp "cannabis use"/ 19012

10 cannab*.tw,kw. 66607

11 Mari?uana*.tw,kw. 23213

12 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla or CBD or indica or cannador).tw,kf. 36267

13 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9)tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex or methylcannabidiol or dimethylcannabidiol).tw,kw. 20078

14 (8063-14-7 or 1972-08-3 or 13956-29-1 or 51022-71-0 or 8001-54-5 or 33086-25-8 or 36557-05-8 or 24359-49-7).rn. 52464

15 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw,kw. 500

16 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw,kw. 27

17 or/4-16146637

18 3 and 17 964

19 exp child/ or exp newborn disease/ or exp infant/ or exp adolescent/ or exp pediatrics/ or abandoned child/ or gifted child/ or orphaned child/ or unwanted child/ or "minor (person)"/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. 6311893

20 18 and 19 517

21 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 1237755

22 Animal experiment/ not (human experiment/ or human/) 2600479

23 21 or 22 2671600

24 20 not 23 484

25 limit 24 to dc=20230101-20240107 100

2.3.14.3.3 CINAHL

Thursday, January 18, 2024, 65111 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S1	(MH "Child Development Disorders, Pervasive") OR (MH "Asperger Syndrome") OR (MH "Autistic Disorder") OR (MH "Pervasive Developmental Disorder-Not Otherwise Specified")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	31,912
S2	TI ("autis*" or "ASD" or "asperger*" or "PDD*" or "pervasive development disorder*" or "childhood disintegrative disorder*") OR AB ("autis*" or "ASD" or "asperger*" or "PDD*" or "pervasive development disorder*" or "childhood disintegrative disorder*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	37,580
S3	S1 OR S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	42,713
S4	(MH "Cannabis") OR (MH "Cannabinoids") OR (MH "Cannabidiol")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	12,855
S5	(MH "Medical Marijuana")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	2,498

			Database - CINAHL Complete	
S6	TI "cannab*" OR AB "cannab*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	15,952
S7	TI Mari#uana* OR AB Mari#uana*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	9,048
S8	TI (“bhang*” or “ganja*” or “ganjah” or “hash” or “hashish” or “hemp*” or “charas” or “sinsemilla”or CBD or indica or cannador) OR AB (“bhang*” or “ganja*” or “ganjah” or “hash” or “hashish” or “hemp*” or “charas” or “sinsemilla” or CBD or indica or cannador)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	4,466
S9	TI ("dronabinol” or “marinol” or “thc” or “tetrahydrocannabinol*” or “tetra-hydrocannabinol*” or “9tetrahydrocannabinol*” or “"Delta (9)tetrahydrocannabinol"“ or “tetrahydrocannabivarin” or “cesamet” or “nabilone” or “nabiximols” or “dexanabinol” or “sativex” or “"hu 211"“ or “hu211” or “"hu 210"“ or “hu210” or “deltanyne” or “cannador*” or “ea 1477” or “ea1477” or “qcd 84924” or “syndros” or “tetranabinex”or methylcannabidiol or dimethylcannabidiol) OR AB ("dronabinol” or “marinol” or “thc” or “tetrahydrocannabinol*” or “tetra-hydrocannabinol*” or “9tetrahydrocannabinol*” or “"Delta (9)tetrahydrocannabinol"“ or	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	2,163

	“tetrahydrocannabivarin” or “cesamet” or “nabilone” or “nabiximols” or “dexanabinol” or “sativex” or “"hu 211"“ or “hu211” or “"hu 210"“ or “hu210” or “deltanyne” or “cannador*” or “ea 1477” or “ea1477” or “qcd 84924” or “syndros” or “tetranabinex”or methylcannabidiol or dimethylcannabidiol)			
S10	TI (“epidiolex” or “gwp 42003p” or “gwp42003p” or “nabidiolex”) OR AB (“epidiolex” or “gwp 42003p” or “gwp42003p” or “nabidiolex”)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	53
S11	TI (“deltanyne” or "abbott 40566" or “namisol” or “dronabinolum” or "QCD 84924" or "CCRIS 4726") OR AB (“deltanyne” or "abbott 40566" or “namisol” or “dronabinolum” or "QCD 84924" or "CCRIS 4726")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	0
S12	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	30,263
S13	S3 AND S12	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	114
S14	((pediatric* OR paediatric* OR (child* NOT childbearing) OR newborn* OR congenital* OR infan* OR baby OR babies	Search modes - Boolean/Phrase	Interface - EBSCOhost Research	1,611,125

	OR neonat* OR "pre-term" OR preterm OR "premature birth*" OR NICU OR preschool* OR "pre-school*" OR kindergarten* OR kindergarden* OR "elementary school*" OR "nursery school*" OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR prepubesc* OR "pre-pubesc*" OR (MH "Child+") OR (MH "Adolescence+") OR (MH "Minors (Legal)") OR "(MH "Child Abuse, Sexual") OR (MH "Child Behavior Disorders+") OR (MH "Child, Medically Fragile") OR (MH "Child Day Care") OR (MH "Child Behavior+") OR (MH "Child Mortality") OR (MH "Child Passenger Safety") OR (MH "Child Development Disorders, Pervasive+") OR (MH "Child Custody") OR (MH "Child Abuse+") OR (MH "Child Nutritional Physiology+") OR (MH "Child Behavior Checklist")) OR SO (child* OR pediatric* OR paediatric* OR adolescent*))		Databases Search Screen - Advanced Search Database - CINAHL Complete	
S15	S13 AND S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	73

2.3.14.3.4. PsycINFO

Thursday, January 18, 2024, 70122 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S1	DE "Autism Spectrum Disorders" OR DE "Autistic Traits"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	57,137
S2	TI ("autis*" or "ASD" or "asperger*" or "PDD*" or "pervasive development disorder*" or "childhood disintegrative disorder*") OR AB ("autis*" or "ASD" or "asperger*" or "PDD*" or "pervasive development disorder*" or "childhood disintegrative disorder*") OR KW ("autis*" or "ASD" or "asperger*" or "PDD*" or "pervasive development disorder*" or "childhood disintegrative disorder*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	70,831
S3	S1 OR S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	71,448
S4	DE "Cannabis" OR DE "Cannabinoids" OR DE "Hashish" OR DE "Marijuana" OR DE "Medical Marijuana"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database -	17,062

			APA PsycInfo	
S5	DE "Cannabinoids" OR DE "Cannabidiol" OR DE "Tetrahydrocannabinol"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	7,341
S6	DE "Marijuana" OR DE "Medical Marijuana"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	4,329
S7	DE "Cannabis Use"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	4,016
S8	DE "Marijuana Legalization"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	742

S9	TI "cannab*" OR AB "cannab*" OR KW "cannab*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	19,842
S10	TI Mari#uana* OR AB Mari#uana* OR KW Mari#uana*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	13,535
S11	TI (“bhang*” or “ganja*” or “ganjah” or “hash” or “hashish” or “hemp*” or “charas” or “sinsemilla”or CBD or indica or cannador) OR AB (“bhang*” or “ganja*” or “ganjah” or “hash” or “hashish” or “hemp*” or “charas” or “sinsemilla” or CBD or indica or cannador) OR KW (“bhang*” or “ganja*” or “ganjah” or “hash” or “hashish” or “hemp*” or “charas” or “sinsemilla”or CBD or indica or cannador)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	2,804
S12	TI ("dronabinol” or “marinol” or “thc” or “tetrahydrocannabinol*” or “tetra-hydrocannabinol*” or “9tetrahydrocannabinol*” or “"Delta (9)tetrahydrocannabinol"“ or “tetrahydrocannabivarin” or “cesamet” or “nabilone” or “nabiximols” or “dexanabinol” or “sativex” or “"hu 211"“ or “hu211” or “"hu 210"“ or “hu210” or “deltanyne” or “cannador*” or “ea 1477” or “ea1477” or “qcd 84924” or “syndros” or “tetranabinex”or methylcannabidiol or dimethylcannabidiol) OR AB ("dronabinol” or “marinol” or “thc” or “tetrahydrocannabinol*” or “tetra-hydrocannabinol*” or “9tetrahydrocannabinol*” or “"Delta	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	3,012

	(9)tetrahydrocannabinol"“ or “tetrahydrocannabivarin” or “cesamet” or “nabilone” or “nabiximols” or “dexanabinol” or “sativex” or “"hu 211"“ or “hu211” or “"hu 210"“ or “hu210” or “deltanyne” or “cannador*” or “ea 1477” or “ea1477” or “qcd 84924” or “syndros” or “tetranabinex”or methylcannabidiol or dimethylcannabidiol) OR KW ("dronabinol” or “marinol” or “thc” or “tetrahydrocannabinol*” or “tetra-hydrocannabinol*” or “9tetrahydrocannabinol*” or “"Delta (9)tetrahydrocannabinol"“ or “tetrahydrocannabivarin” or “cesamet” or “nabilone” or “nabiximols” or “dexanabinol” or “sativex” or “"hu 211"“ or “hu211” or “"hu 210"“ or “hu210” or “deltanyne” or “cannador*” or “ea 1477” or “ea1477” or “qcd 84924” or “syndros” or “tetranabinex” or methylcannabidiol or dimethylcannabidiol)			
S13	TI (“epidiolex” or “gwp 42003p” or “gwp42003p” or “nabidiolex”) OR AB (“epidiolex” or “gwp 42003p” or “gwp42003p” or “nabidiolex”) OR KW (“epidiolex” or “gwp 42003p” or “gwp42003p” or “nabidiolex”)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	33
S14	TI (“deltanyne” or "abbott 40566" or “namisol” or “dronabinolum” or "QCD 84924" or "CCRIS 4726") OR AB (“deltanyne” or "abbott 40566" or “namisol” or “dronabinolum” or "QCD 84924" or "CCRIS 4726") OR KW (“deltanyne” or "abbott 40566" or “namisol” or “dronabinolum” or "QCD 84924" or "CCRIS 4726")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	1
S15	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced	33,409

			Search Database - APA PsycInfo	
S16	S3 AND S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	135
S17	(DE "Adolescent Development" OR DE "Childhood Development") OR DE "Pediatrics" OR (DE "Congenital Disorders" OR DE "Agenesis" OR DE "Cleft Palate" OR DE "Drug Induced Congenital Disorders" OR DE "Hermaphroditism" OR DE "Microcephaly" OR DE "Prader Willi Syndrome" OR DE "Spina Bifida")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	168,673
S18	DE "Child Characteristics" OR DE "child abuse" OR (DE "Child Welfare" OR DE "Child Guidance" OR DE "Child Labor" OR DE "Missing Children")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	54,704
S19	(DE "chronically ill children" OR DE "child neglect" OR DE "child psychopathology" OR DE " child psychiatry") OR (DE "Child Care" OR DE "Child Care Workers" OR DE "Child Day Care" OR DE "Child Self Care")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database -	30,648

			APA PsycInfo	
S20	(TX pediatric* or paediatric* or (child* not childbearing) or newborn* or congenital* or infan* or baby or babies or neonat* or pre term or preterm* or premature birth or NICU or preschool* or pre school* or kindergarten* or kindergarden* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or prepubesc* or pre pubesc*) OR (SO child* or adolesc* or pediat* or paediat*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	1,551,785
S21	S17 OR S18 OR S19 OR S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	1,552,681
S22	S16 AND S21	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	68
S23	(RD 20230101- OR ZD "in process")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	199,986

S24	S22 AND S23	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	10

2.3.14.3.5 The Cochrane Library

Date Run 18/01/2024 191759

ID	Search	Hits
#1	MeSH descriptor [Cannabis] this term only	526
#2	MeSH descriptor [Cannabinoids] explode all trees	1210
#3	MeSH descriptor [Cannabaceae] this term only	0
#4	MeSH descriptor [Medical Marijuana] this term only	46
#5	MeSH descriptor [Marijuana Use] explode all trees	427
#6	MeSH descriptor [Marijuana Smoking] this term only	365
#7	(cannab*)ti,ab,kw	4687
#8	(Mari?uana*)ti,ab,kw	2374
#9	(bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla or CBD or indica or cannador)ti,ab,kw	4676
#10	(dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9)tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex or methylcannabidiol or dimethylcannabidiol)ti,ab,kw	2211
#11	(deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726")ti,ab,kw	22
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	9656
#13	MeSH descriptor [Child Development Disorders, Pervasive] explode all trees	2562
#14	(autis* or ASD or asperger* or PDD* or pervasive development* disorder* or childhood disintegrative disorder* or CDD or Heller* syndrome or disintegrative psychosis)ti,ab,kw	6697
#15	#13 OR #14	6697
#16	#12 AND #15	51
#17	MeSH descriptor [Child] explode all trees	79062
#18	MeSH descriptor [Congenital, Hereditary, and Neonatal Diseases and Abnormalities] explode all trees	31106
#19	MeSH descriptor [Infant] explode all trees	42298
#20	MeSH descriptor [Adolescent] this term only	126257
#21	MeSH descriptor [Pediatrics] explode all trees	1180

#22 MeSH descriptor [Child, Abandoned] this term only 7

#23 MeSH descriptor [Child, Exceptional] this term only 1

#24 MeSH descriptor [Child, Orphaned] this term only 46

#25 MeSH descriptor [Child, Unwanted] this term only 0

#26 MeSH descriptor [Minors] this term only 11

#27 pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc* 451162

#28 (child* or adolesc* or pediat* or paediat*)so 50063

#29 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 OR #25 OR #26 OR #27 OR #28 461981

#30 #16 AND #29 39

For Trials, Filter to Date added to CENTRAL trials database Custom range 01/01/2023-18/01/2024

2.3.14.3.6 Web of Science Core Collection

 # Web of Science Search Strategy (v0.1)

 # Database Web of Science Core Collection

Entitlements

- WOS.SCI 1900 to 2024

- WOS.AHCI 1975 to 2024

- WOS.ESCI 2019 to 2024

- WOS.ISTP 1990 to 2024

- WOS.SSCI 1956 to 2024

- WOS.ISSHP 1990 to 2024

 # Searches

1 TS=(autis* OR ASD OR asperger* OR PDD* OR "pervasive development* disorder*" OR "childhood disintegrative disorder*" OR CDD OR "Heller* syndrome" OR "disintegrative psychosis") Date Run Thu Jan 18, 2024, 113152 GMT-0800 (Pacific Standard Time) Results 132736

2 TS=(cannab* OR Mari?uana* OR bhang* OR ganja* OR ganjah OR hash OR hashish OR hemp* OR charas OR sinsemilla OR CBD OR indica OR cannador) Date Run Thu Jan 18, 2024, 113205 GMT-0800 (Pacific Standard Time) Results 164884

3 TS=(dronabinol OR marinol OR thc OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol* OR "Delta (9)tetrahydrocannabinol" OR tetrahydrocannabivarin OR cesamet OR nabilone OR nabiximols OR dexanabinol OR sativex OR "hu 211" OR hu211 OR "hu 210" OR hu210 OR deltanyne OR cannador* OR "ea 1477" OR ea1477 OR "qcd 84924" OR syndros OR tetranabinex OR methylcannabidiol OR dimethylcannabidiol)

Date Run Thu Jan 18, 2024, 113216 GMT-0800 (Pacific Standard Time)

Results 21650

4 TS=(epidiolex OR "gwp 42003p" OR gwp42003p OR nabidiolex)

Date Run Thu Jan 18, 2024, 113227 GMT-0800 (Pacific Standard Time)

Results 161

5 TS=(deltanyne OR "abbott 40566" OR namisol OR dronabinolum OR "QCD 84924" OR "CCRIS 4726")

Date Run Thu Jan 18, 2024, 113239 GMT-0800 (Pacific Standard Time)

Results 9

6 (TS=(cannab* OR Mari?uana* OR bhang* OR ganja* OR ganjah OR hash OR hashish OR hemp* OR charas OR sinsemilla OR CBD OR indica OR cannador)) OR (TS=(dronabinol OR marinol OR thc OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol* OR "Delta (9)tetrahydrocannabinol" OR tetrahydrocannabivarin OR cesamet OR nabilone OR nabiximols OR dexanabinol OR sativex OR "hu 211" OR hu211 OR "hu 210" OR hu210 OR deltanyne OR cannador* OR "ea 1477" OR ea1477 OR "qcd 84924" OR syndros OR tetranabinex OR methylcannabidiol OR dimethylcannabidiol)) OR (TS=(epidiolex OR "gwp 42003p" OR gwp42003p OR nabidiolex))

Date Run Thu Jan 18, 2024, 113315 GMT-0800 (Pacific Standard Time)

Results 174634

7 (TS=(deltanyne OR "abbott 40566" OR namisol OR dronabinolum OR "QCD 84924" OR "CCRIS 4726"))

Date Run Thu Jan 18, 2024, 113344 GMT-0800 (Pacific Standard Time)

Results 9

8 (TS=(autis* OR ASD OR asperger* OR PDD* OR "pervasive development* disorder*" OR "childhood disintegrative disorder*" OR CDD OR "Heller* syndrome" OR "disintegrative psychosis"))

Date Run Thu Jan 18, 2024, 113359 GMT-0800 (Pacific Standard Time)

Results 132736

9 #7 OR #6 OR #5 OR #4 OR #3 OR #2

Date Run Thu Jan 18, 2024, 113410 GMT-0800 (Pacific Standard Time)

Results 174635

10 #9 AND #1

Date Run Thu Jan 18, 2024, 113525 GMT-0800 (Pacific Standard Time)

Results 388

11 ALL=((pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR pre-term OR preterm* OR "premature birth*" OR NICU OR preschool* OR pre-school* OR kindergarten* OR kindergarden* OR "elementary school*" OR "nursery school*" OR ("day care*" NOT adult*) OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR pre-pubesc* OR prepubesc*))

Date Run Thu Jan 18, 2024, 113603 GMT-0800 (Pacific Standard Time)

Results 5489964

12 SO=((child* OR adolesc* OR pediat* OR paediat*))

Date Run Thu Jan 18, 2024, 113626 GMT-0800 (Pacific Standard Time)

Results 414028

13 #12 OR #11

Date Run Thu Jan 18, 2024, 113643 GMT-0800 (Pacific Standard Time)

Results 5490637

14 #10 AND #13

Date Run Thu Jan 18, 2024, 113713 GMT-0800 (Pacific Standard Time)

Results 222

2.3.14.3.7 Google Scholar

autism|autistic|asperger
cannabis|marijuana|dronabinol|marinol|cannabinol|cannabidiol|cannabinoid
pediatric|child|children|adolescent|infant

First 200 results retrieved only

2.3.14.3.8 WHO International Clinical Trials Registry Platform (ICTRP)

Condition Autism AND Intervention cannabis OR marijuana OR dronabinol OR marinol OR cannabinol OR cannabidiol OR cannabinoid

Filter Search for clinical trials in children

Recruitment Status = ALL

9 Results

2.3.14.3.9 ClinicalTrials.gov

Autism | Cannabis | Applied Filters Child (birth–17) – 7 Results

Autism | marijuana | Applied Filters Child (birth–17) – 7 Results

Autism | dronabinol | Applied Filters Child (birth–17) – 1 Results

Autism | Marinol| Applied Filters Child (birth–17) – 1 Results

Autism | cannabidiol| Applied Filters Child (birth–17) – 0 Results

Autism | cannabidiol| Applied Filters Child (birth–17) – 7 Results

Autism | cannabinoid | Applied Filters Child (birth–17) – 3 Results

26 results total

2.3.14.3.10 Scopus Conference Abstracts

((TITLE-ABS-KEY (autis* OR asd OR asperger* OR pdd* OR "pervasive development* disorder*" OR "childhood disintegrative disorder*" OR cdd OR "Heller* syndrome" OR "disintegrative psychosis")) AND (TITLE-ABS-KEY (cannab* OR mari?uana* OR bhang* OR ganja* OR ganjah OR hash OR hashish OR hemp* OR charas OR sinsemilla OR cbd OR indica OR cannador)) OR (TITLE-ABS-KEY (dronabinol OR marinol OR thc OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol* OR "Delta (9)tetrahydrocannabinol" OR tetrahydrocannabivarin OR cesamet OR nabilone OR nabiximols OR dexanabinol OR sativex OR "hu 211" OR hu211 OR "hu 210" OR hu210 OR deltanyne OR cannador* OR "ea 1477" OR ea1477 OR "qcd 84924" OR syndros OR tetranabinex OR methylcannabidiol OR dimethylcannabidiol)) OR (TITLE-ABS-KEY (epidiolex OR "gwp 42003p" OR "gwp42003p" OR nabidiolex) OR TITLE-ABS-KEY (deltanyne OR "abbott 40566" OR namisol OR dronabinolum OR "QCD 84924" OR "CCRIS 4726")) AND (TITLE-ABS-KEY (pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR pre-term OR preterm* OR "premature birth*" OR nicu OR preschool* OR pre-school* OR kindergarten* OR kindergarden* OR "elementary school*" OR "nursery school*" OR ("day care*" not AND adult*) OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR pre-pubesc* OR prepubesc*) OR SRCTITLE (child* OR adolesc* OR pediat* OR paediat*))) AND (LIMIT-TO (DOCTYPE , "cp") OR LIMIT-TO (DOCTYPE , "cr"))

7 Results

Papers First (OCLC)

(kw autism OR kw autistic OR kw asperger*) AND (kw canna* OR kw marijuana OR kw dronabinol OR kw marinol) AND (kw pediatric* OR kw paediatric* OR kw child* OR kw adolescen* OR kw infan*)

0 results

2.3.14.3.11 Proceedings (OCLC)

(kw autism n10 canna*) OR (kw autistic n10 canna*) OR (kw asperger* n10 canna*) OR (kw autism n10 marijuana) OR (kw autistic n10 marijuana) OR (kw asperger* n10 marijuana) OR (kw autism n10 dronabinol) OR (kw autistic n10 dronabinol) OR (kw asperger* n10 dronabinol) OR (kw autism n10 marinol) OR (kw autistic n10 marinol) OR (kw asperger* n10 marinol) AND (kw pediatric* OR kw paediatric* OR kw child* OR kw adolescen* OR kw infan*)

0 results

2.3.14.3.12 ProQuest Theses and Dissertations Global

noft(autism OR autistic OR asperger*) AND noft(canna* OR marijuana OR dronabinol OR marino) AND noft(pediatric* OR paediatric* OR child* OR adolescen* OR infan*)

8 results

2.3.14.3.13 Networked Digital Library of Theses and Dissertations (NDLTD)

subject"autism" AND subject"cannabis" – 0 results

title"autism" AND title"cannabis" – 0 results

subject"autistic" AND subject"cannabis"

title"autistic" AND title"cannabis"

subject"cannabidiol" AND subject"autism"

title"cannabidiol" AND title"autism"

All 0 results

Section 2.4 Safety of cannabinoids used for medical purposes in children A systematic review and meta-analysis

2.4.1 Overview

In LSR, we identified RCTs investigating the safety and efficacy of cannabinoid use in children with various indications; however, no systematic review and meta-analysis reported on a comprehensive adverse event profile of cannabinoids in children. In this systematic review and meta-analysis, we studied the adverse event profile of cannabinoids used for medical purposes in children and adolescents. We pooled cannabinoid-related adverse events data in children reported across randomized controlled trials. We also conducted a subgroup analysis based on the indication for cannabinoid use, intervention duration, and the study population's age.

We attempted to provide comprehensive evidence on adverse events associated with cannabinoid use for medical purposes in children and adolescents from 23 RCTs. All adverse event outcomes were extracted from each trial and pooled as a risk ratio with a 95% Confidence interval.

Safety of cannabinoids used for medical purposes in children A systematic review and meta-analysis

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Manuscript status

Published

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2.4.2 Abstract

IMPORTANCE Cannabinoids are increasingly used for medical purposes in children. Evidence of the safety of cannabinoids in this context is sparse, creating a need for reliable information to close this knowledge gap.

OBJECTIVE To study the adverse event profile of cannabinoids used for medical purposes in children and adolescents.

DATA SOURCES For this systematic review and meta-analysis, MEDLINE, Embase, PsycINFO, and the Cochrane Library were searched for randomized clinical trials published from database inception to March 1, 2024, for subject terms and keywords focused on cannabis and children and adolescents. Search results were restricted to human studies in French or English.

STUDY SELECTION Two reviewers independently performed the title, abstract, and full-text review, data extraction, and quality assessment. Included studies enrolled at least 1 individual 18 years or younger, had a natural or pharmaceutical cannabinoid used as an intervention to manage any medical condition, and had an active comparator or placebo.

DATA EXTRACTION AND SYNTHESIS Two reviewers performed data extraction and quality assessment independently. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and PRISMA-S guideline were used. Data were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES The primary outcome was the incidence of withdrawals, withdrawals due to adverse events, overall adverse events, and serious adverse

events in the cannabinoid and control arms. Secondary outcomes were the incidence of specific serious adverse events and adverse events based on organ system involvement.

RESULTS Of 39 175 citations, 23 RCTs with 3612 participants were included (635 [17.6%] female and 2071 [57.3%] male; data not available from 2 trials); 11 trials (47.8%) included children and adolescents only, and the other 12 trials (52.2%) included children, adolescents, and adults. Interventions included purified cannabidiol (11 [47.8%]), nabilone (4 [17.4%]), tetrahydrocannabinol (3 [13.0%]), cannabis herbal extract (3 [13.0%]), and dexanabinol (2 [8.7%]). The most common indications were epilepsy (9 [39.1%]) and chemotherapy-induced nausea and vomiting (7 [30.4%]). Compared with the control, cannabinoids were associated with an overall increased risk of adverse events (risk ratio [RR], 1.09; 95% CI, 1.02-1.16; I2 = 54%; 12 trials), withdrawals due to adverse events (RR, 3.07; 95% CI, 1.73-5.43; I2 = 0%;14 trials), and serious adverse events (RR, 1.81; 95% CI, 1.21-2.71; I2 = 59%; 11 trials). Cannabinoid-associated adverse events with higher RRs were diarrhea (RR, 1.82; 95% CI, 1.30-2.54; I2 = 35%; 10 trials), increased serum levels of aspartate aminotransferase (RR, 5.69; 95% CI, 1.74-18.64; I2 = 0%; 5 trials) and alanine aminotransferase (RR, 5.67; 95% CI, 2.23-14.39; I2 = 0%; 6 trials), and somnolence (RR, 2.28; 95% CI, 1.83-2.85; I2 = 8%; 14 trials).

CONCLUSION AND RELEVANCE In this systematic review and meta-analysis, cannabinoids used for medical purposes in children and adolescents in RCTs were associated with an increased risk of adverse events. The findings suggest that long-term safety studies, including those exploring cannabinoid-related drug interactions and tools that improve adverse event reporting, are needed.

KEYWORDS Cannabinoids; children; safety; adverse events; cannabidiol; tetrahydrocannabinol; nabilone

2.4.3 Key Points

Question What is the adverse event profile of cannabinoids used for medical purposes in children and adolescents?

Findings In this systematic review and meta-analysis of 23 randomized clinical trials including 3612 participants, cannabinoids used for medical purposes in children and adolescents were associated with increased risk of adverse events, serious adverse events, and withdrawals due to adverse events compared with the control group.

Meaning The findings suggest that physicians considering cannabinoids for medical purposes in children and adolescents should weigh the risk and benefit profile of cannabinoids and available therapeutic options as well as the individual's underlying disease condition and prognosis.

2.4.4 Introduction

Cannabinoids have been used for medical purposes since antiquity.(1) In response to increased interest and expanding literature about the use of cannabinoids for medical purposes in in children, adolescents, and adults,(2, 3) many jurisdictions have updated their medical cannabis (MC) laws and regulations.(4) Children and adolescents with complex health challenges, including drug-resistant epilepsy (DRE), cancer, chronic pain, autism spectrum disorder (ASD), and tuberous sclerosis complex (TSC), are increasingly being administered cannabinoids with or without authorization from their healthcare practitioners.(5, 6)

Cannabidiol (CBD) and tetrahydrocannabinol (THC) are just two examples of more than 100 phytocannabinoids derived from the genus *Cannabis* and are the most abundant cannabinoids produced by the plant.(1, 7, 8) In Canada, cannabinoids, including THC and CBD are available for purchase in the form of cannabis herbal extracts (CHE), sprays, gummies, dried herb, and topical formulations.(7, 9) Nabilone, dronabinol, and dexanabinol are pharmaceutical-grade cannabinoids used for medical purposes that have received marketing authorizations for various indications in adults.(10) Cannabidiol oral solution is a plant derived highly purified pharmaceutical grade CBD indicated for use as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or TSC in patients 1-2 years of age and older depending on jurisdiction.(11, 12) Various cannabinoid products have been associated with improved outcomes and quality of life in children with certain conditions, such as DRE,(13-15) chemotherapy-induced nausea, and vomiting (CINV),(10) ASD,(16-19) cerebral palsy (CP),(20) and traumatic brain injury (TBI).(20, 21)

Concomitantly, concerns have been raised regarding the safety of cannabis use for medical purposes in children.(22)·(23) As medical cannabis use in children has become more

prevalent and cannabinoids are associated with an increased risk of adverse events when co-administered with other drugs,(24) which frequently occurs in pediatric conditions(25) where cannabis use is reported, adverse events warrant investigation.

Several randomized controlled trials (RCTs) have evaluated the safety and efficacy of cannabinoids in children with DRE,(13-15) ASD,(16, 17) cerebral palsy,(20) TBI,(20, 21) and cancer.(10) However, to our knowledge, have comprehensively summarized the safety outcomes across cannabinoid products (including medical cannabis and pharmaceutical cannabinoids) in children. Previous work focused on the safety of unique cannabinoids and conditions;(26) did not include children and adolescents only or did not synthesize the data in a meta-analysis.(27) We conducted a systematic review and meta-analysis summarizing the adverse events profile of cannabinoids used for medical purposes in children from all relevant RCTs; the results can be used to inform decision-making in clinical practice.

2.4.5 Methods

2.4.5.1 Eligibility Criteria and Outcomes

The protocol for this systematic review and meta-analysis was registered with PROSPERO (CRD42020187433) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline,(28) PRISMA-S(29) guidelines, and the reporting items of the Cochrane Collaboration.(30) We included studies that enrolled at least one child aged < 18 years, with a natural or pharmaceutical cannabinoid used as an intervention to manage any medical condition. RCTs of all designs were considered with an active comparator, or placebo. The primary outcome was the incidence of withdrawals, withdrawals due to adverse events, overall adverse events, and serious adverse events in the

cannabinoid vs. the control arm (placebo or active control). The secondary outcomes were the incidence of specific serious adverse events and adverse events based on organ systems.

2.4.5.2 Search strategy

An experienced health sciences librarian (M.-L.L.) searched 4 databases from inception to March 1, 2024, MEDLINE Embase, PsycInfo, and the Cochrane Library. The search was designed to be broad and included subject terms and keywords focused on the primary concepts of cannabis (hemp, marijuana, CBD, etc.) and children and adolescents (kids, adolescents, teenagers, etc.). The complete search strategies used to search the databases are available in the Supplementary files and elsewhere.(31) The search strategy was peer-reviewed by another librarian using the Peer-Review of Electronic Search Strategies checklist.(32) International Clinical Trials Registry Platform, ClinicalTrials.gov, gray literature, and manual searches were also performed to identify potential studies. All search results were deduplicated in EndNote (Clarivate) and then imported into Covidence.(33)

2.4.5.3 Study selection, data extraction, and quality assessment

A pair of reviewers (M.C. and M.B.-E.) independently performed abstract and full-text screening, data extraction, and quality assessment in Covidence. Disagreements between the reviewers were resolved by a third reviewer (L.E.K.). Data were extracted for the characteristics of the included studies, study participants, serious adverse events, withdrawals, withdrawals due to adverse events, overall adverse events, and specific adverse events. The internal validity of the included RCTs was assessed using the Cochrane Risk of Bias tool.(34)

2.4.5.4 Data synthesis and analysis

The analyses were conducted using the metabin package in R Studio, version 2023.06.0 + 421 (R Project for Statistical Computing) using R programming. All adverse event outcomes were extracted from each trial and pooled as a risk ratio (RR) with a 95% CI using the Der Simonian and Laird method for the random-effects model.(35) Statistical heterogeneity was assessed using Q statistics.(36) In the case of heterogeneity (I2>50%), subgroup analysis was conducted based on the indication for cannabinoid use, duration of intervention, and the age of the study population. Publication bias was evaluated by examining serious adverse events and withdrawals (≥10 trials) using a funnel plot.(37)

2.4.6 Results

2.4.6.1 *Characteristics of included studies and participants*

Of 39 175 identified citations, 23 RCTs (15 parallel trials, 7 cross-over trials, and 1 adaptive dose-finding trial) were included (15-17, 20, 21, 38-55) with 3612 participants (635 [17.6%] female and 2071 [57.3%] male; data not available from 2 trials). One article(40) was comprised of 2 crossover RCTs. **Figure 2.4.1.** illustrates the study selection process using the PRISMA flow diagram. The included trials were conducted between 1979 to 2022,(15-17, 20, 21, 38-55) and 12 included trials (52.2%) were multicentric.(15, 20, 21, 39, 42, 45, 46, 48, 49, 51, 52, 54) Trials were conducted in different countries, including 12 (52.2%) in the US,(15, 21, 39, 42-46, 48, 51, 52, 55), 8 (78.3%) in Australia(15, 21, 38-41, 51, 52), 8 (78.3%) in the UK,(20, 42, 45-47, 50-52) 6 (26.1%) in Israel,(16, 20, 21, 39, 52, 54) 5 (21.7%) in the Netherlands, (39, 48, 49, 51, 52) 5 (21.7%) in Spain, (39, 46, 49, 51, 52) 4 (17.4%) in Poland,(45, 48, 51, 52) 3 (13.0%) in France,(45, 46, 52) and 1 (4.3%) each in Canada,(53) Sweden,(49) New Zealand,(15) the Czech Republic,(20) and Brazil.(17)

Of the 23 trials, 11 (47.8%) included children and adolescents (n=1199) exclusively,(15-17, 20, 38-40, 42, 45, 47, 51-53) and the remaining 12 (52.2%) included both children and adults.(21, 41, 43, 44, 46, 48-50, 54, 55) The common indications for cannabinoids in children were DREs (9[39.1%]; including Lennox-Gastaut syndrome, Dravet syndrome, TSC, and Fragile X syndrome),(15, 39, 42, 45, 46, 48, 49, 51, 52) followed by CINV (7 [30.4%]),(40, 41, 43, 44, 47, 53, 55) ASD (3 [13.0%]),(16, 17, 38) TBI (2 [8.6%]),(21, 54) spasticity (1 [4.3%]),(20) and cannabis use disorder (1 [4.3%]).(50) Purified CBD (11 [47.8%]),(15, 38, 39, 42, 45, 46, 48-52) nabilone (4 [17.4%]),(43, 44, 47, 53) THC (3 [13.0%]),(40, 41, 55) CHEs (3 [13.0%]),(16, 17, 20) and dexanabinol (2 [8.7%])(21, 54) were used as interventions in included trials. **Table 2.4.1.** presents the characteristics of the included studies and their participants. A critical appraisal of the included trials by the Cochrane ROB tool revealed most trials had an unclear risk of bias (11 [47.8%])(15, 21, 38, 40-44, 49, 54, 55) followed by a low risk (9 [39.1%])(16, 20, 39, 42, 45, 48, 50-52) and a high risk (3 [13.0%]).(17, 47, 53) In trials with unclear risk of bias, there was lack of information on blinding of outcome assessors (detection bias), study participants, and allocation concealment. **eFigure 2.4.1.** and **eFigure 2.4.2.** illustrate the quality assessment of trials.

2.4.6.2 Primary outcomes

The RR of developing adverse events in the cannabinoid group was higher (RR, 1.09; 95% CI, 1.02-1.16; I2 = 54%; 12 trials) than that in the control group (**Figure 2.4.2.**). To address the heterogeneity of 54%, a subgroup analysis was conducted and products containing CBD only were separated from those containing CBD and THC. Subgroup analysis revealed a higher RR for developing adverse events in the cannabinoid group compared with the control group in trials with purified CBD (RR, 1.11; 95% CI, 1.03-1.19; I2 = 58%; 9 trials), cannabinoid treatment

duration of more than 12 weeks (RR, 1.11; 95% CI, 1.02- 1.21; I2 = 66%; 6 trials), trials that included children and adolescents along with adults (RR, 1.24; I2 = 0%; 95% CI, 1.11-1.39; I2 = 6%; 3 trials), and epilepsy trials (RR, 1.11; 95% CI, 1.02- 1.20; I2 = 62%; 8 trials). Compared with the control, cannabinoids were not associated with risk (RR, 1.28; 95% CI, 0.99-1.67; I2 = 34%; 16 trials) of withdrawals from trials (**Figure 2.4.3**.). In the subgroup analysis, there was a higher RR for the withdrawal of participants from trials with purified CBD (RR, 3.29; 95% CI, 1.83-5.90; I2 = 15%; 9 trials) compared with CHEs (RR, 1.00; 95% CI, 0.39-2.58; I2 = 0%; 1 trial), for which there was no association with withdrawal. There was also a higher RR for withdrawal of participants from the trial with a population with epilepsy (RR, 3.81; 95% CI, 1.97-7.38; I2 = 0%; 6 trials) and with cannabinoid treatment duration of more than 12 weeks (RR, 3.55; 95% CI, 1.77-7.13; I2 = 33%; 7 trials). **Table 2.4.2.** presents the results of subgroup analysis based on cannabinoid type, study population, and cannabinoid treatment duration.

In the subgroup analysis, there was a higher RR for the withdrawal of participants from trials with purified CBD (RR3.29, 95%CI 1.83-5.90; $I^2$15, 9 trials) compared to CHE (RR1, 95%CI 0.39-2.58, $I^2$0%, 1 trial), in populations with epilepsy (RR3.81, 95%CI 1.97-7.38, $I^2$0%, 6 trials), and a cannabinoid treatment duration of ≥12 weeks (RR3.55, 95%CI 1.77-7.13; $I^2$33%, 7 trials). **Table 2.4.2.** presents the results of subgroup analysis based on cannabinoid type, study population, and cannabinoid treatment duration.

Cannabinoids were associated with a higher risk of serious adverse events (RR, 1.81; 95% CI, 1.21-2.71; I2 = 59%; 11 trials) (**eFigure 2.4.3.**). Specific cannabinoid-related serious adverse events for which there was similar risk in the cannabinoid and control arms included serum levels of aspartate aminotransferase (AST) (RR, 4.80; 95% CI, 0.88-26.29; I2 = 0%;3 trials), alanine aminotransferase (ALT) (RR, 4.22; 95% CI, 0.75-23.75; I2 = 0%; 3 trials), both

aminotransferases (RR, 2.19; 95% CI, 0.39-12.19; I2 = 40%; 4 trials), acute respiratory failure (RR, 2.14; 95% CI, 0.22-20.40; I2 = 0%; 2 trials), pneumonia (RR, 1.80; 95% CI, 0.35-9.23; I2 = 0%; 2 trials), and status epilepticus (RR, 1.08; 95% CI, 0.38-3.07; I2 = 0%; 5 trials) (**eTable 2.4.1.**). Based on subgroup analysis, in trials including children and adolescents only (RR, 1.87; 95% CI, 1.30- 2.70; I2 = 9%; 7 trials), evaluating purified CBD (RR, 2.16; 95% CI, 1.55-3.02; I2 = 8%; 8 trials), with a cannabinoid treatment duration of more than 12 weeks (RR, 2.30; 95% CI, 1.57-3.38; I2 = 27%; 6 trials), and in which participants had a diagnosis of epilepsy (RR, 2.16; 95% CI, 1.55-3.02; I2 = 8%; 8 trials), cannabinoids were associated with a higher risk of serious adverse events than control arms. The risk of withdrawals due to adverse events in the cannabinoid group was higher (RR, 3.07; 95% CI, 1.73-5.43; I2 = 0%; 14 trials) than in the control group (**eFigure 2.4.4**). **eFigures 2.4.5 and 2.4.6** 1 illustrate inverted funnel plots for adverse events and serious adverse events.

2.4.6.3 Secondary outcomes

With regard to gastrointestinal system–related adverse events, a decrease in appetite (RR, 1.61; 95% CI, 1.08-2.41; I2 = 62%; 13 trials) and increases in diarrhea (RR, 1.82; 95% CI, 1.30-2.54; I2 = 35%; 10 trials) and dry mouth (RR, 2.40; 95% CI, 1.85- 3.10; I2 = 0%; 4 trials) were reported in the cannabinoid group compared with the control group. Central nervous system (CNS)–related adverse events in the cannabinoid group that were significantly higher than in the control group were sedation (RR, 4.78; 95% CI, 1.42-16.07; I2 = 0%; 3 trials), dizziness (RR, 2.57; 95% CI, 1.13-5.86; I2 = 51%; 5 trials), euphoria (RR, 4.89; 95% CI, 1.93-12.35; I2 = 65%; 6 trials), and somnolence (RR, 2.28; 95% CI, 1.83-2.85; I2 = 8%; 14 trials). Cannabinoid treatment was also associated with increased risk of blurred vision (RR, 4.85; 95% CI, 2.92-8.03; I2 = 0%; 2 trials), increased serum levels of AST (RR, 5.69; 95% CI, 1.74-18.64; I2 = 0%; 5

trials), increased serum levels of ALT (RR, 5.67; 95% CI, 2.23- 14.39; I2 = 0%; 6 trials), fatigue (RR, 1.67; 95% CI, 1.22-2.30; I2 = 25%; 8 trials), and lethargy (RR, 1.81; 95% CI, 1.16-2.83; I2 = 0%; 3 trials). Adverse events for which there was similar risk in the intervention and control arms were headache (RR, 0.65; 95% CI, 0.39-1.07; I2 = 0%; 4 trials), depression (RR, 0.79; 95% CI, 0.49-1.27; I2 = 0%; 2 trials), gastroenteritis (RR, 0.86; 95% CI, 0.11-6.87; I2 = 69%; 3 trials), convulsion (RR, 0.63; 95% CI, 0.04-10.20; I2 = 78%; 2 trials), hypotension (RR, 0.83; 95% CI, 0.31-2.24; I2 = 66%; 3 trials), and psychomotor hyperactivity (RR, 0.29; 95% CI, 0.04-2.19; I2 = 0%; 2 trials).

eTable 2.4.2. describes a comprehensive list of reported adverse events based on the organ system of involvement. Adverse events that were reported in only 1 trial (number of included study participants in the cannabinoid group vs control group) included nausea (4.6% [4 of 86] vs 3.5% [3 of 85]), bloating (5.1% [3 of 59] vs 0%), hyperglycemia (23.3% [7 of 30] vs 16.2% [6 of 37]), and weight loss (12.2% [23 of 188] vs 3.2% [3 of 94]). **eTable 2.4.3** in describes the complete list of adverse events reported in only 1 trial.

2.4.7 Discussion

This systematic review and meta-analysis provides comprehensive evidence on adverse events associated with cannabinoids used for medical purposes in children and adolescents from 23 RCTs. Compared with the control group, cannabinoids were associated with a higher risk of developing adverse events, serious adverse events, and withdrawals due to adverse events, particularly in RCTs of epilepsy, when treatment duration was more than 12 weeks, in trials using purified CBD, and in trials that enrolled only children and adolescents.

Purified CBD, nabilone, THC, and CHE were used for medical purposes in the RCTs.(15-17, 20, 21, 38-55) Purified CBD was used in children with refractory epilepsy in 11 RCTS with a duration ranging between 10 and14 weeks.(15, 39, 42, 45, 46, 48-52) Use of purified CBD was associated with an increased risk of overall adverse events, including serious adverse events, withdrawals, and withdrawals due to adverse events compared with CHEs.(39, 42, 45, 46, 48-52) This finding could be due to a tendency to use higher doses of purified CBD.

In trials on purified CBD, children continued at least 3 antiepileptic drugs, including clobazam, valproate, levetiracetam, and benzodiazepines.(42, 45, 48, 51, 56) Cannabidiol interferes with the metabolism of other drugs by inhibiting cytochrome (CYP) 3A4, CYP1A2, CYP2C9, and CYP2C19 isoenzymes.(25) Concomitant administration of CBD with clobazam and other antiepileptic drugs has been associated with increased risk of CNS-related adverse events (somnolence, euphoria, sedation, and dizziness) in children.(57, 58) Further research reported that coadministration of CBD and clobazam did not decrease seizure frequency and severity.(59) CBD inhibits the metabolism of the toxic metabolite of clobazam, N-desmethylclobazam (nCLB) by inhibiting CYP2C19 and CYP3A4 enzymes.(57, 58) An observational study reported an adverse event rate of 77% with this combination due to higher N-desmethylclobazam plasma levels.(57)

While the effects of THC on the endocannabinoid system are well documented, the pharmacologic mechanisms of how CBD induces adverse events remain to be elucidated.(60) For example, CBD may interfere with immune cell function and has been associated with increased risk of infections, although this was not shown in our analysis.(60) Our pooled analysis revealed the risk of elevated serum aminotransferase levels (both ALT and AST) and γ-glutamyl transferase levels in the cannabinoid (specifically CBD) group compared with the control arm.

Previous research has documented significant serum aminotransferase level elevations of greater than 3 times higher than normal.(45) In our included trials, CBD was present in CHEs along with THC in varying CBD and THC ratios, making it impossible to establish a unique dose response to each.(16, 17) Cannabidiol reduces the clearance of THC, thus increasing potential for adverse reactions to THC.(25) Cannabinoids were associated with gastrointestinal-related adverse events in the included studies, including decrease in appetite and dry mouth. These adverse events were short term and resolved with continued use.

Nabilone and THC were used as interventions to manage CINV in children and adolescents.(40, 41, 43, 44, 47, 53, 55) These trials were conducted in the 1980s, with a common duration ranging between 18 and 25 chemotherapy cycles, and had a high risk of bias.(40, 41, 43, 44, 47, 53, 55) Tetrahydrocannabinol was associated with euphoria, mood changes, fatigue, dizziness, and decreased concentration compared with the control group.(40, 41, 55) This meta-analysis evaluated short-term adverse effects only, and we could not draw conclusions on the long-term effects of cannabinoid exposures on the developing brain. This remains an area of significant concern as the endocannabinoid system plays a major role in brain development, starting prenatally and extending into childhood.(61, 62) Components of the endocannabinoid system, including cannabinoid receptor 1, are found in the fetal brain as early as 16 to 22 days' gestation and are believed to play a major role in neuronal differentiation, migration, and synaptogenesis, especially in the prefrontal cortex and limbic system.(63, 64)

While long-term adverse effects of prenatal recreational cannabis exposures have been documented, there remains a paucity of data when medical cannabis is used in children.(63, 65) The brain and endocannabinoid system continue to develop during childhood and adolescence, increasing vulnerability to development of long-term neuronal changes.(66)

Tetrahydrocannabinol may have an effect on brain development in children by altering white and gray matter distribution as well as on cognition.(61, 62) Cannabinoid receptor 1 is concentrated in brain regions, including the prefrontal cortex, cerebellum, basal ganglia, hippocampus, amygdala, and cingulate cortex.(67, 68) Imaging studies have shown differences in the distribution of white matter in adolescents with recreational cannabis exposure compared with non-exposure.(69) However, consideration should be given to the differences in THC dosing between recreational cannabis (mostly inhaled dried and high in THC) and medical cannabis products used following physician recommendations, which typically start with CBD-enriched extracts. Recreational cannabis use often lacks characterization of product type, route of administration, or dose.(70)

In this study, the clinical significance of reported adverse events associated with medical cannabis was short term and most adverse events were defined as non-severe. Our findings suggest that physicians and caregivers should monitor children and adolescents receiving medical cannabis for adverse events, such as somnolence, changes in appetite, dizziness, and other cannabinoid-related adverse events. Nevertheless, physicians considering medical cannabis in children and adolescents should weigh the risk and benefits of cannabinoids and available therapeutic options along with the individual's underlying condition and prognosis. Physicians should also be cognizant that cannabinoids can interact with other drugs, especially when children and adolescents are receiving CBD and antiepileptic drugs, such as clobazam and sodium valproate. Children and adolescents treated with CBD and clobazam should be closely monitored for CNS-related adverse events, such as lethargy, fatigue, and somnolence, secondary to altered clobazam metabolism, and lowering of the clobazam dose accordingly should be considered.

Overall, the available safety information for each unique cannabinoid product is sparse, and safety data are missing for many pediatric indications for which cannabinoid use has been reported. The Canadian Paediatric Society has recently released a position statement, which includes a comprehensive literature review on the indications, benefits, and practical recommendations.(71) While converging lines of evidence suggest that there are long-term effects of recreational (high THC) cannabis use (e.g., on brain development and architecture),(72, 73) there is limited high-quality data to inform short-term harms or risk mitigation plans for children and adolescents using cannabinoids for medical purposes.

The lack of long-term safety data on medical cannabis in children and adolescents can make it challenging for physicians to manage the care of children and adolescents with complex health conditions receiving medical cannabis and to mitigate its potential associated risks. Strategies to improve reporting practices for cannabinoid-related serious adverse event or reaction detection and management in clinical trials are critical for informing safety plans and communicating risks to families. Further research on the long-term effects of medical cannabis used for medical purposes in children and adolescents is needed, along with education for physicians and families on potential risks and harm reduction approaches. In the meantime, the potential risk of neurodevelopmental sequela must be weighed in the context of the potential for negative neurodevelopmental sequelae resulting from an unmet medical need (such as DRE) and the risks related to other available treatment options for children and adolescents.

2.4.7.1 Strengths and Limitations

This systematic review and meta-analysis has strengths. The study followed rigorous methods; an extensive search strategy (peer reviewed per the Peer Review of Electronic Search Strategies checklist), screening, data extraction, and quality assessment were performed

independently in duplicate. To our knowledge, this is the first systematic review that pooled cannabinoid-related adverse events across different indications from RCTs among children and adolescents.

This study has limitations that impacted our ability to make inferences to inform clinical care. First, there was methodologic heterogeneity in trial designs, indications, interventions, dose, and duration. The duration of most of the included trials was short (10-14 weeks or 1-2 cycles of anticancer therapy), creating a gap in evidence regarding the long-term safety of cannabinoids in children and adolescents. The paucity of reports on concomitant drugs administered to children and adolescents limited our ability to evaluate drug interactions. Second, there is no standardized method or tool to capture cannabinoid-related adverse events in children and adolescents, leading to inconsistencies in definitions and grading. As such, we were unable to summarize cannabinoid-related adverse events based on severity. For example, lethargy, fatigue, somnolence, and sedation terms were used across studies and may be difficult for participants to differentiate without clear definitions and grading criteria. Adverse events were reported in studies as serious adverse events, but little information was provided about how these events were graded or how causality was determined. Third, there were discrepancies (based on dose or treatment group) between how serious adverse events were reported. To address this, we summed the adverse events from the different doses in the cannabinoid group. Limitations to interpreting these findings include that few included studies evaluated CHEs, thus highlighting a need for a pathway for global research efforts to identify the safety and benefits of these cannabis-based products.

2.4.8 Conclusion

This systematic review and meta-analysis of 23 RCTs involving children and adolescents receiving cannabinoids for medical purposes revealed an increased risk of adverse events, serious adverse events, and withdrawals due to adverse events compared with controls. Cannabinoids were also associated with drug interactions, such as CBD and antiepileptic drugs (e.g., clobazam, sodium valproate) and benzodiazepines. The findings suggest that physicians and caregivers supporting children and adolescents taking cannabinoids should actively monitor for adverse events.

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2.4.10 Author contribution statement

Dr Kelly had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design Chhabra, Ben-Eltriki, Kelly. Acquisition, analysis, or interpretation of data All authors. Drafting of the manuscript Chhabra, Kelly. Intellectual content All authors. Statistical analysis Chhabra, Ben-Eltriki, Kelly. Obtained funding Kelly. Administrative, technical, or material support Le.

Supervision Ben-Eltriki, Finkelstein, Kelly. Critical review of the manuscript for important All authors.

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2.4.12 Figures

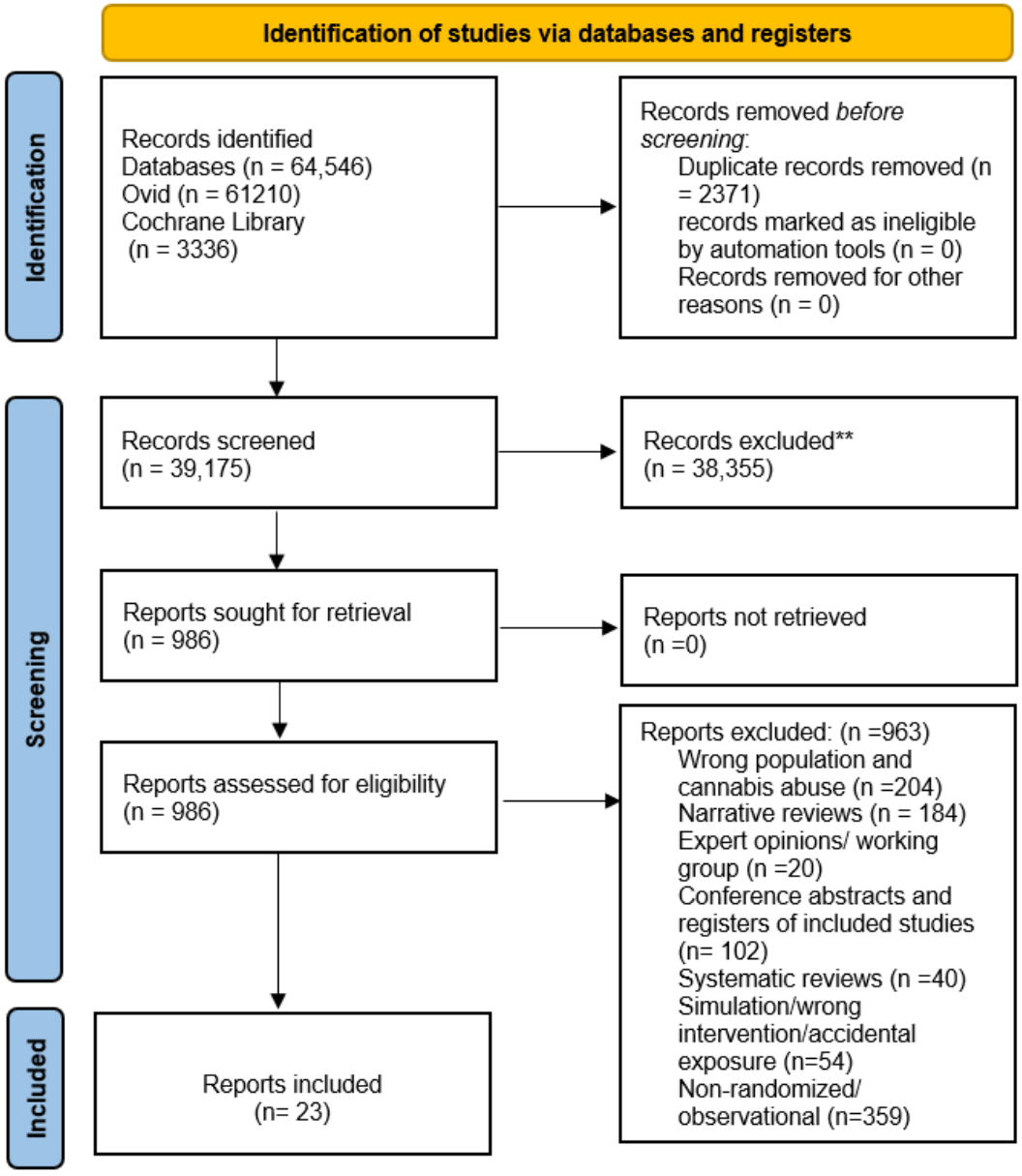
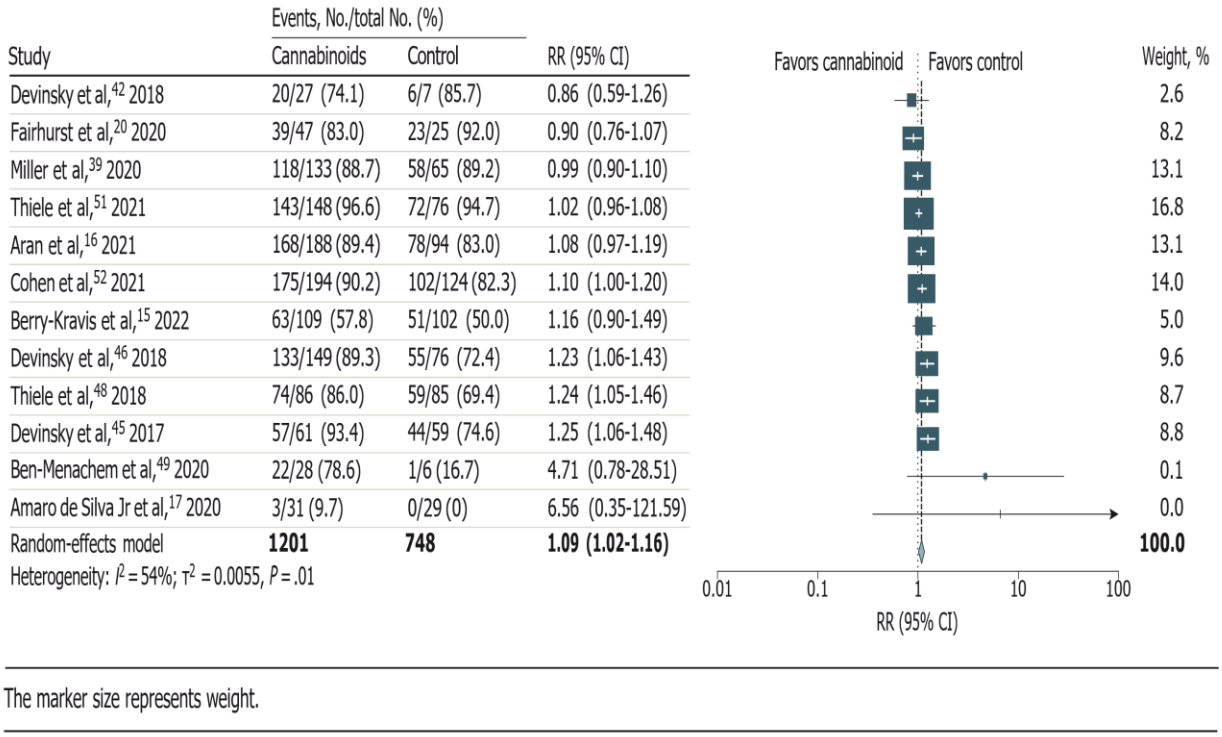
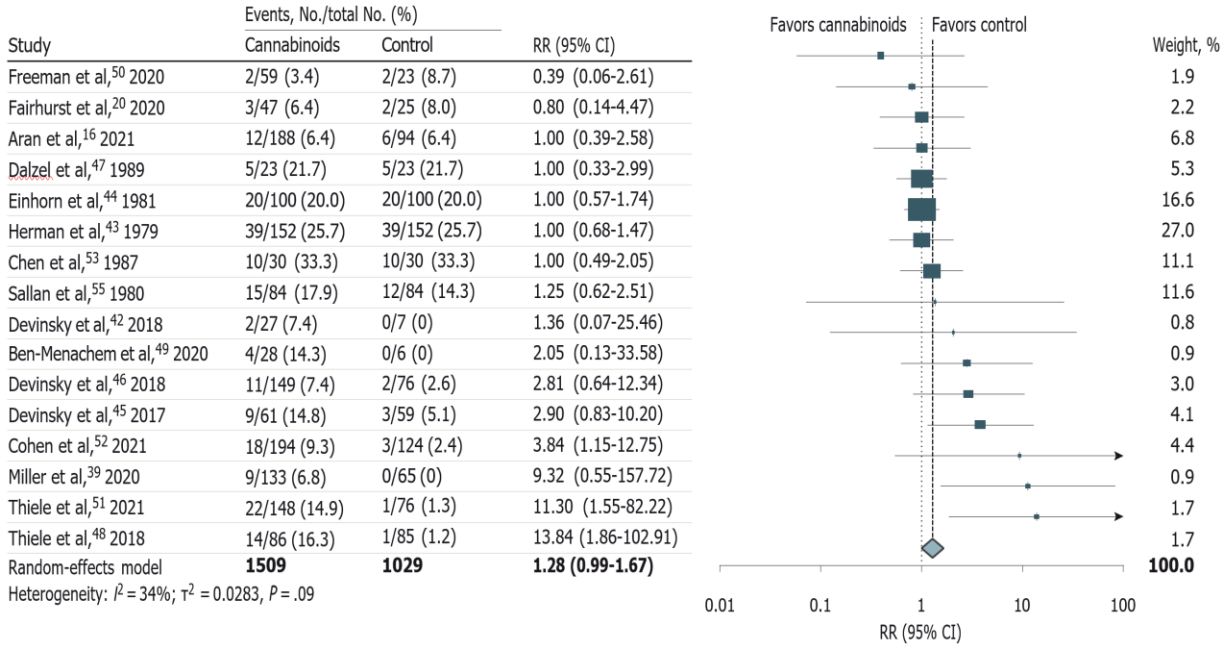


Figure 2.4.1. The PRISMA flow diagram for the final inclusion of studies.



The marker size represents weight.

Figure 2.4.2. Comparison of the risk ratio of adverse events between cannabinoid and control groups.



The marker size represents weight.

Figure 2.4.3. Comparison of the risk ratio of withdrawals from trials between cannabinoid and control groups.

2.4.13 Tables

Table 2.4.1. Characteristics of the included randomized controlled trials and study participants.

Author	Study centre, sites, and Countries	Trail design	Indication	Age, Mean SD or Median (range),	No. (%)	Intervention	Control	Total number of patients	Duration of treatment and safety follow-up	Cannabinoid used, dose
Efron et al,(38) 2021	Australia (1)	RCT	Intellectual Disability	8-16; median, 13.5 (range, 11-16.6)	3 (37.5)/5 (62.5)	Purified CBD solution	Placebo	purified CBD 4, Placebo 4	Treatment 8 wk	Purified CBD extract (98%), 20 mg/kg per d to 500 mg/d
Fairhurst et al,(20) 2020	UK, Israel, and the Czech Republic (14)	RCT	Spasticity due to CP or TBI	8-18; mean (SD), 12.7 (3.4)	28 (38.8)/44 (61.1)	Nabiximol, CBD and THC spray (2525.7)	Placebo	Nabiximol 47, Placebo 25	Treatment 12 wk	Nabiximol, CBD and THC spray (2.5 2.7), 12 spray/d CBD 30 mg/d, THC32.4 mg/d
Aran et al, (16) 2021	Israel (1)	Crossover	ASD	5-21 years, (range) 11.3 (range, 5.1-20.8)	30 (20)/120 (70)	CBD-enriched CHE, purified CBD, and THC	Placebo	CBD-enriched cannabis extract group (201) 95, purified CBD and THC 93, placebo 94	Treatment 12 wk. washout 4 wk	CBD-enriched cannabis extract group (201), purified CBD and THC (CBD 167 mg/mL and THC 8.35 mg/mL), children weighing 20-40 kg CBD 1 mg/kg per d, THC 0.05 mg/kg per d, children >40 kg max CBD 420 mg/d and max THC 21 mg/d
Miller et al, (39) 2020	US, Australia, Spain, the Netherlands, and Israel	RCT	Convulsive seizures in Dravet	2-18; mean (SD), 9.6 (4.6)	104 (52.5)/94 (47.5)	Purified CBD solution	Placebo	Purified CBD 133 (CBD10 66, CBD20 67), placebo 59	Treatment 14 wk; safety follow-up 4 wk	Purified CBD solution, 10 and 20 mg/kg per d

	(43), and Israel		syndrome							
Silva et al, (17) 2022	Brazil	RCT	ASD	5-11; mean (SD), 7.68 (1.74)	8 (13.33)/52 (86.67)	CBD-enriched CHE	Placebo	CBD-enriched cannabis extract group 31, control group 29	Treatment 12 wk	CBD-enriched cannabis herbal extract, CBD THC 91, CBD 0.9-21 mg/d, THC 0.1-1.75 mg/d
Ekert et al, (40) 1979a and b	Studies 1 and 2 Australia (1)	Studies 1 and 2 crossover	Studies 1 and 2 CINV	Studies 1 and 2 5-19. median, 11	Study 1 4 (21)/15 (79), study 2 7 (50)/7 (50)	Studies 1 and 2 Δ-9-THC	Study 1 metoclopramide, study 2 PCPZ	Study 1 metoclopramide, study 2 PCPZ	Study 1 Δ-9-THC 17, placebo 25, study 2 Δ-9-THC 18, PCPZ 18	Study 1 Δ-9-THC 10 mg/m2, maximum dose 15 mg, given at 2, 4, 8, 16, and 24 h around chemotherapy administration, study 2 Δ-9-THC 10 mg/m2, maximum dose 15 mg, given at 2, 4, 8, 16, and 24 h around chemotherapy administration
Sallan et al, (55) 1980	US (1)	Crossover	CINV	9-70; median, 32.5	33 (39.2)/51 (60.8)	Δ-9-THC	PCPZ	84 Randomized, 28 received Δ-9-THC and PCPZ in crossover trial (assessed for safety)	Three 1-d courses of either 2 Δ-9-THC and 1 PCPZ or 2 PCPZ and 1 Δ-9-THC	Δ-9-THC 10 mg/m2, PCPZ 10-mg tablet
Chang et al, (41) 1979	Australia (1)	RCT	CINV in patients with osteogenic sarcoma receiving	15-49. median, 24	5 (33.33)/10 (66.7)	Δ-9-THC	Placebo	Δ-9-THC 15, placebo 15	3 Doses of Δ-9-THC for 6 chemotherapy cycles of methotrexate	Δ-9-THC 10 mg/m2 given orally every 3 h for a total of 5 doses

			high-dose methotrexate chemotherapy							
Devinsky et al, 2018a (42)	US and UK (11)	RCT	Dravet syndrome	4-10; mean (SD), 7.6 (1.8)	18 (53.4)/16 (47.0)	Purified CBD solution	Placebo	Purified CBD 27 (CBD5 10, CBD10 8, CBD20 9), placebo 7	Treatment 3 wk; safety follow-up 4 wk	Purified CBD solution, 5, 10, and 20 mg/kg per d
Herman et al, (43) 1979	US (1)	Crossover	CINV	15-74. median, 33	26 (17)/126 (83)	Nabilone	PCPZ	Nabilone 152, PCPZ 152	NA	Nabilone 2 mg every 6 hour
Einhorn et al, (44) 1981	US (1)	Crossover	CINV	15-74. median, 28	NA/NA	Nabilone	PCPZ	Nabilone 80, PCPZ 80	76 courses	Nabilone 2 mg every 6h as needed
Devinsky et al, (45) 2017	US, France, Poland, and UK (23)	RCT	Drug-resistant seizures in Dravet syndrome	2-18; mean (SD), 9.8 (4.8)	58 (48)/62 (52)	Purified CBD solution	Placebo	Purified CBD 61, Placebo 59	Treatment 14 wk; safety follow-up 4 wk	Purified CBD solution 20 mg/kg per d
Devinsky et al, (46) 2018b	US, UK, Spain, and France (30)	RCT	Drop seizures in Lennox-Gastaut Syndrome	2-55; mean (SD), 15.3 (9.3)	96 (42.6)/129 (57.4)	Purified CBD solution	Placebo	Purified CBD 149 (CBD 10 mg 73, CBD 20 mg 76), placebo 76	Treatment 14 wk; safety follow-up 4 wk	Purified CBD solution, 10 and 20 mg/kg per d
Dalzell et al, (47) 1989	UK (1)	Crossover	CINV	10 mo-17 y	4 (17.3)/19 (82.7)	Nabilone	Domperidone	Nabilone 23, placebo 23	22 cycles of chemotherapy	<18 kg 0-5 mg twice a day, 18-36 kg

										1 mg twice a day, >36 kg 1 mg 3 times a day 15 mg 3 times a day 15 mg three times a day
Thiele et al, (48) 2018	US, the Netherlands, and Poland (24)	RCT	Lennox-Gastaut Syndrome	2-55; mean (SD), 15.4 (9.2)	83 (48.5)/88 (51.5)	Purified CBD solution	Placebo	Purified CBD 86, placebo 85	Treatment 14 wk	purified CBD solution, 2.5-20 mg/kg/day
Ben-Menachem et al, (49) 2020	Spain, Sweden, the Netherlands (5)	RCT	Epilepsy	16-55; mean (SD), 29.5 (10.5) y	12 (35)/22 (65)	Purified CBD solution and Stripentol, purified CBD solution and Valproic acid	Placebo	Purified CBD 25 (purified CBD + stiripentol 14, purified CBD solution + valproic acid 21), placebo 6	Treatment 5 wk; follow-up 4 wk	Purified CBD solution, 20 mg/kg per d
Freeman et al, (50) 2021	UK (1)	Adaptive bayesian dose-finding	Cannabis use disorder	16-26, placebo 24.87, 200-mg CBD 27.33, 400-mg CBD 26.58, 800-mg CBD 27.43	23 (28)/59 (72)	Purified CBD	Placebo	200-mg CBD 12, 400-mg CBD 24, 800-mg CBD 23, placebo 23	Treatment 1-4 wk. safety 16 wk	Purified CBD at dose of 200, 400, and 800 mg
Thiele et al, (51) 2021	US, Poland, Australia, Spain, the Netherlands, and UK (46)	RCT	Drug-resistant seizures in TSC	1-65; median, 11.4 (range, 1.1-56.8)	93 (41.5)/121 (58.5)	Purified CBD solution	Placebo	Purified CBD 148 (CBD 25 75, CBD 50 73), placebo 76	Treatment 29.5 wk (treatment period 16 wk, stable dosing 12 wk, 10-d taper); safety	Purified CBD solution, 5-50 mg/kg per d

									follow-up 4 wk	
Madan Cohen et al, (52) 2021	US, France, Poland, UK, Australia, Spain, the Netherlands, and Israel (22 and 43)	RCT	Dravet syndrome	2-18; mean, 9.7 (range, 2.2- 18.9)	162 (50.9)/156 (49.1)	Purified CBD solution	Placebo	Purified CBD 194, placebo 124	Treatment 14 wk; safety follow-up 4 wk	Purified CBD solution, 10-20 mg/kg per d
Chan et al, (53) 1987	Canada (1)	Crossover	CINV	3.5-17.8. mean, 11.8	NA/NA	Nabilone	PCPZ	Nabilone 30, PCPZ 30	2 Cycles	Nabilone, 2 mg, 2-3 times a day
Knoller et al, (54) 2002	Israel (1)	RCT	Severe TBI	16-65; mean, dexanabinol, mean (SD) 31 (13); placebo, mean (SD), 29 (12)	10 (15)/57 (85)	Dexanabinol Injection	Placebo	Dexanabinol 30, placebo 37	1-Time injection, day 10 and 1, 3, and 6 mo	Single dexanabinol injection, 48 or 150 mg
Maas et al, (21) 2005	Australia, Europe, Israel, and US (100)	RCT	Severe TBI	16-65; mean, dexanabinol, 32, placebo, 33	157 (18)/689 (82)	Dexanabinol Injection	Placebo	Dexanabinol 428, placebo 418	1-Time injection, 6 mo	Single dexanabinol injection, 48 or 150 mg
Berry-Kravis et al, (15) 2022	US, Australia, and New Zealand (21)	RCT	Fragile X syndrome	3-17; mean, 9.7	53 (25)/159 (75)	Purified CBD transdermal gel	Placebo	Purified CBD transdermal gel 102, placebo 109	12-wk treatment	Purified cannabidiol transdermal gel ≤35 kg 250 mg/d, >35 kg 500 mg/d

Abbreviations ASD Autism Spectrum Disorder, CP Cerebral Palsy, RCT Randomized Controlled Trial, CBD Cannabidiol, CINV Chemotherapy Induced Nausea and Vomiting, TBI Traumatic Brain Injury, THC Tetrahydrocannabinol, TSC Tuberous Sclerosis Complex

Table 2.4.2 Subgroup analysis of the RR of adverse events, withdrawals due to adverse events, withdrawals and serious adverse events in the cannabinoid group compared to the control.

		Events, No./total No. (%)			
Outcome	**Trials No.**	**Cannabinoids**	**Control**	**Risk ratio (95% CI)**	**I2, %**
Adverse events					
Cannabinoid type					
CBD-enriched cannabis extract	2	171/219 (78.0)	78/123 (63.4)	1.44 (0.39-5.27)	32
Purified CBD	9	805/935 (86.1)	448/600 (74.7)	1.11 (1.03-1.19)	58
Nabiximol	1	39/47 (83.0)	23/25 (92.0)	0.90 (0.76-1.07)	0
Duration of study, wk					
<10	2	42/55 (76.4)	7/13 (53.8)	1.59 (0.32-7.85)	69
10-12	4	273/375 72.8)	152/250 (60.8)	1.04 (0.91-1.18)	43
>12	6	700/771 (90.8)	390/485 (80.4)	1.11 (1.02-1.21)	66
Indication					
Epilepsy	8	742/826 (89.8)	397/498 (79.7)	1.11 (1.02-1.20)	62
Autism Spectrum disorder	2	171/219 (78.1)	78/123 (63.4)	1.44 (0.39-5.27)	32
Fragile X syndrome	2	171/219 (78.1)	78/123 (63.4)	1.44 (0.39-5.27)	32
Population					
Children and adolescents	9	786/938 (83.8)	434/581 (74.7)	1.05 (0.99-1.11)	41
Children, adolescents, and adults	3	229/263 (87.1)	115/167 (68.8)	1.24 (1.11-1.39)	6
Withdrawals					
Cannabinoid type					
CBD-enriched cannabis extract	1	12/188 (6.4)	6/94 (6.4)	1.00 (0.39-2.58)	0
Purified CBD	9	91/885 (10.3)	12/521 (2.3)	3.29 (1.83-5.90)	15
Nabiximol	1	3/47 (6.4)	2/25 (8.0)	0.80 (0.14-4.47)	0
Nabilone	4	74/305 (24.3)	74/305 (24.3)	1.00 (0.76-1.32)	0
Δ-9-THC	1	15/84 (17.9)	12/84 (14.3)	1.25 (0.62-2.51)	0
Duration of study, wk					
<10	7	95/444 (21.4)	86/402 (21.4)	1.04 (0.80-1.34)	0
10-12	2	15/235 (6.4)	8/119 (6.7)	0.95 (0.41-2.18)	0
>12	7	85/830 (10.2)	12/508 (2.4)	3.55 (1.77-7.13)	33
Indication					

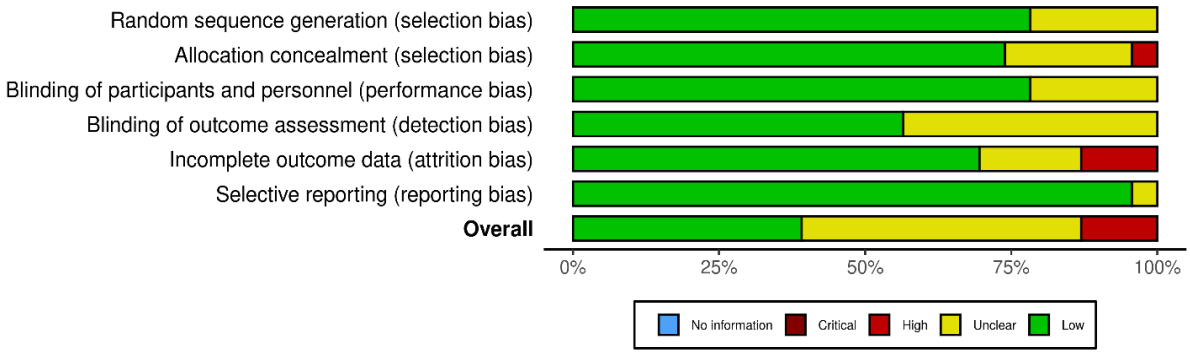
Autism spectrum disorder	1	12/188 (6.4)	6/94 (6.4)	1.00 (0.39-2.58)	0
Epilepsy	6	73/713 (10.2)	9/406 (2.2)	3.81 (1.97-7.38)	0
Lennox-Gastaut syndrome	2	16/113 (14.2)	1/92 (1.1)	5.61 (0.61-51.36)	39
Spasticity	1	3/47 (6.4)	2/25 (8.0)	0.80 (0.14-4.47)	0
CINV	5	89/389 (22.9)	86/389 (22.1)	1.03 (0.80-1.34)	0
Cannabis use disorder	1	2/59 (3.4)	2/23 (8.7)	0.39 (0.06-2.61)	0
Population					
Children and adolescents	9	90/851 (10.6)	30/503 (6.0)	1.68 (0.98-2.87)	33
Children, adolescents, and adults	7	105/658 (16.0)	76/526 (14.4)	1.11 (0.85-1.46)	37
Withdrawals due to adverse events					
Cannabinoid type					
CBD-enriched cannabis extract	1	2/188 (1.1)	1/94 (1.1)	1.00 (0.09-10.89)	0
Purified CBD	8	62/826 (7.5)	6/498 (1.2)	4.07 (1.95-8.49)	0
Nabiximol	1	2/47 (4.3)	0/25	2.68 (0.13-53.81)	0
Nabilone	4	13/315 (4.1)	4/315 (1.3)	2.38 (0.76-7.50)	0
Duration of study, wk					
<10	6	18/370 (4.9)	4/328 (1.2)	2.02 (0.80-5.09)	0
10-12	2	4/235 (1.7)	1/119 (0.8)	1.47 (0.23-9.50)	0
>12	6	57/771 (7.4)	6/485 (1.2)	4.74 (2.15-10.41)	0
Indication					
Autism spectrum disorder	1	2/188 (1.1)	1/94 (1.1)	1.00 (0.09-10.89)	0
Epilepsy	6	52/713 (7.3)	5/406 (1.2)	3.99 (1.76-9.03)	0
Lennox-Gastaut syndrome	2	10/113 (8.8)	1/92 (1.1)	4.42 (0.82-23.80)	0
Spasticity	1	2/47 (4.2)	0/25	2.68 (0.13-53.81)	0
CINV	4	13/315 (4.1)	4/315 (1.3)	2.38 (0.76-7.50)	0
Population					
Children and adolescents	9	53/861 (6.2)	5/513 (1.0)	3.56 (1.68-7.55)	0
Children, adolescents, and adults	5	26/515 (5.0)	6/419 (1.4)	2.58 (1.03-6.43)	0
Serious adverse events					
Cannabinoid type					
CBD-enriched cannabis extract	1	5/188 (2.7)	1/94 (1.1)	2.50 (0.30-21.09)	0
Purified CBD	8	158/826 (19.1)	40/498 (8.0)	2.16 (1.55-3.02)	8

Nabiximol	1	4/47 (8.5)	3/25 (12.0)	0.71 (0.17-2.92)	0
Dexanabinol	1	175/428 (40.9)	167/418 (40.0)	1.02 (0.87-1.21)	0
Traumatic brain	1	175/428 (40.9)	167/418 (40.0)	1.02 (0.87-1.21)	0
Population					
Children and adolescents	7	119/798 (14.9)	33/450 (7.3)	1.87 (1.30-2.70)	9
Children, adolescents, and adults	4	223/691 (32.3)	178/585 (30.4)	1.81 (0.82-3.99)	72
Duration of study, wk					
<10	3	181/483 (37.5)	168/431 (39.0)	1.02 (0.87-1.20)	0
10-12	2	9/235 (3.8)	4/119 (3.4)	1.04 (0.32-3.39)	0
>12	6	152/771 (19.7)	39/485 (8.0)	2.30 (1.57-3.38)	27
<10	3	181/483 (37.5)	168/431 (39.0)	1.02 (0.87-1.20)	0

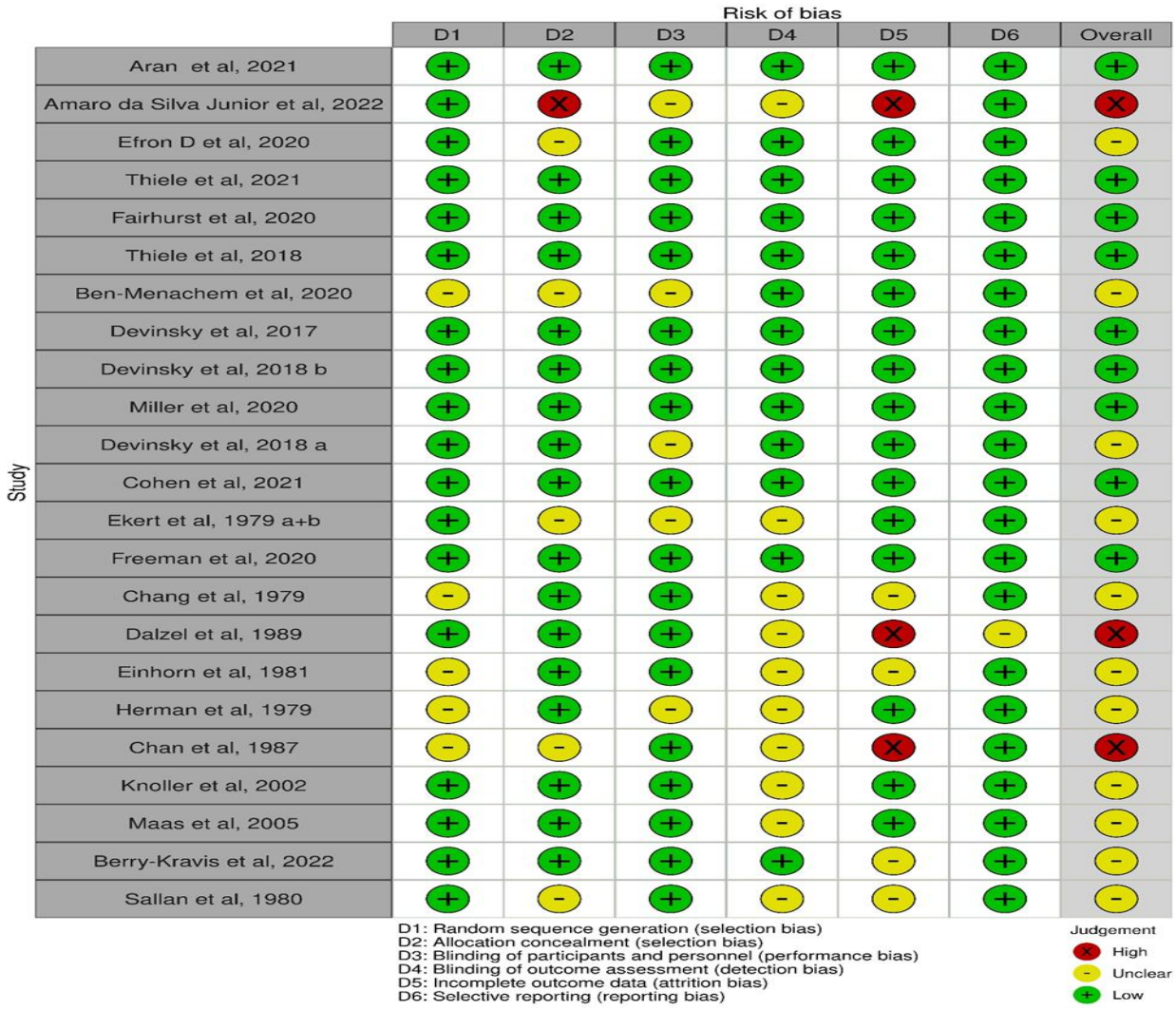
Abbreviations CBD, cannabidiol; CINV, chemotherapy-induced nausea and vomiting.

2.4.14 Supplementary material

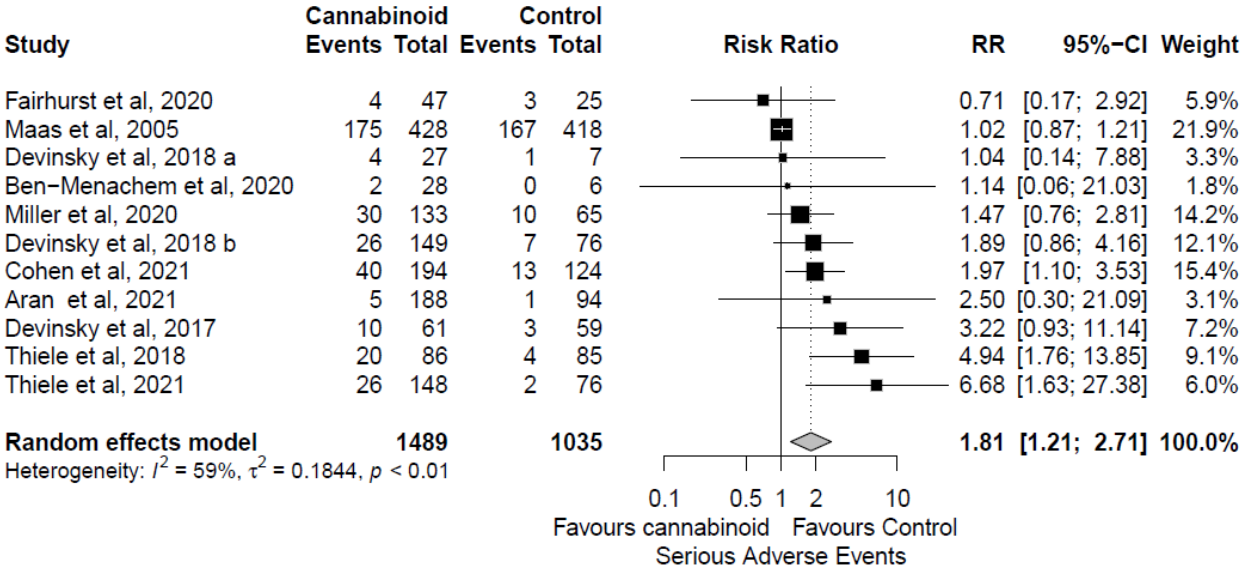
2.4.14.1 eFigures



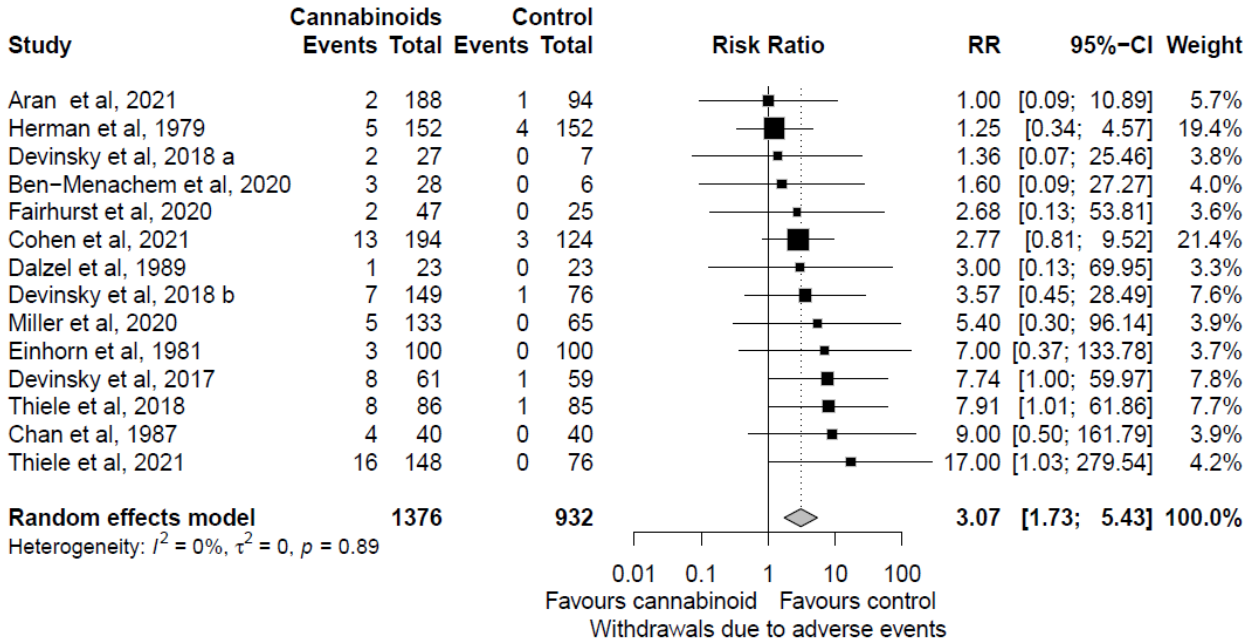
eFigure 2.4.1. Risk of bias based on the judgement of reviewers for the included studies.



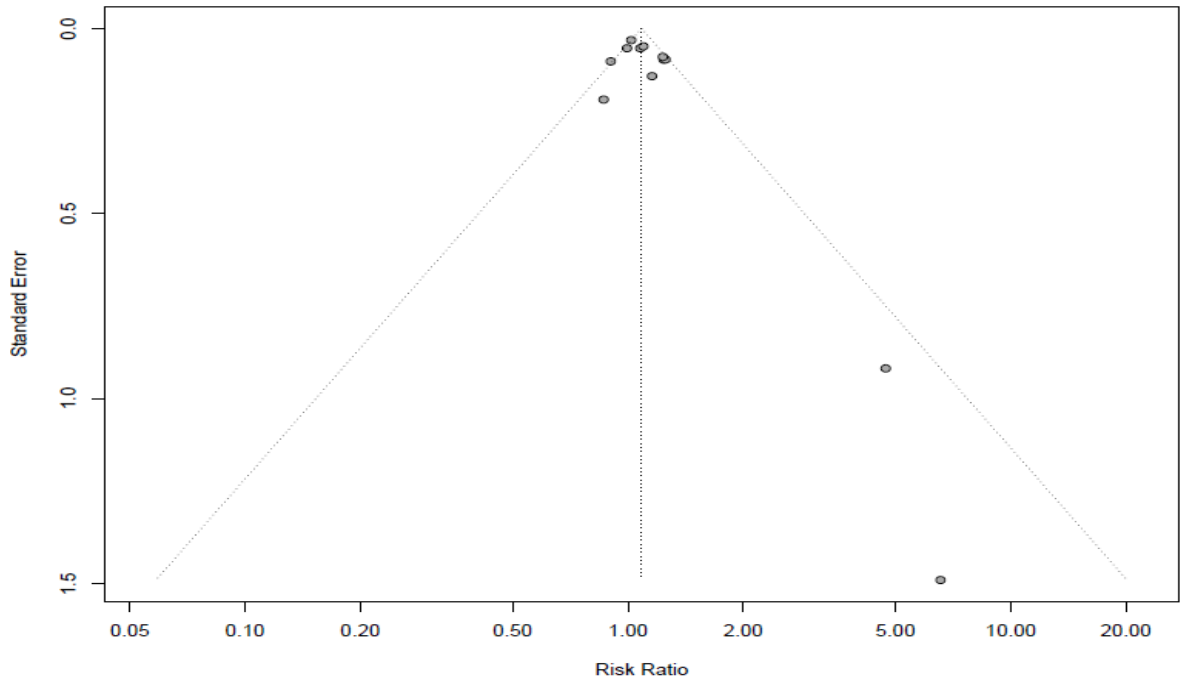
eFigure 2.4.2. Summary of the risk of bias of the included randomized controlled trials.



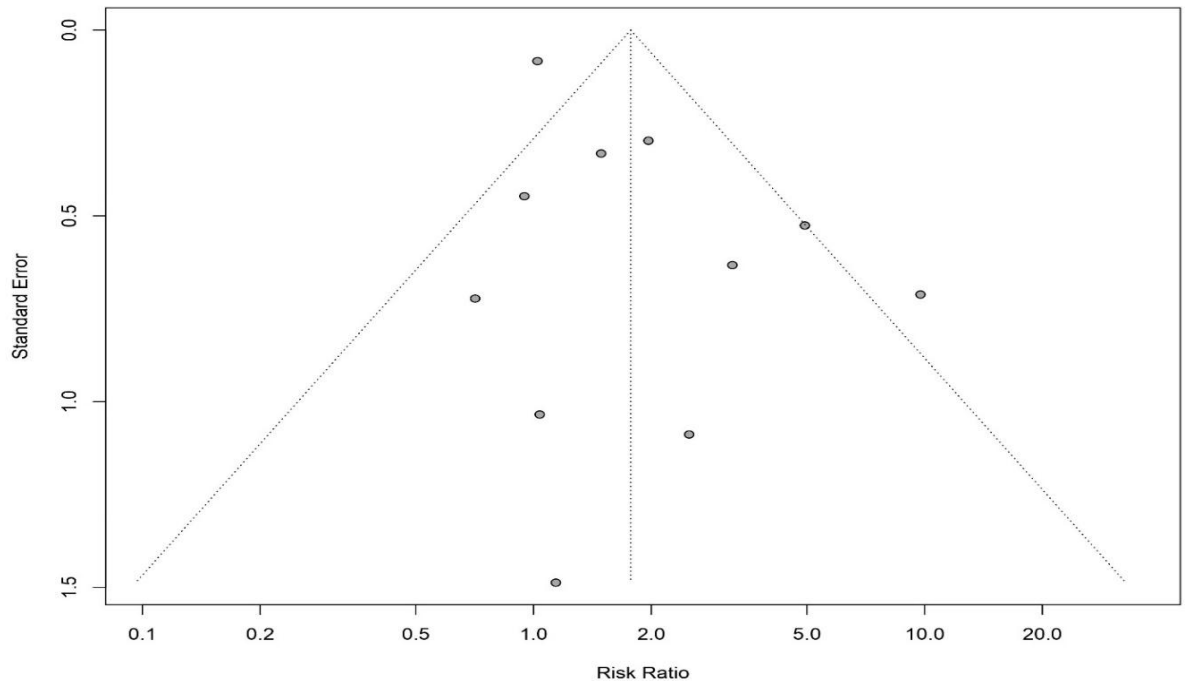
eFigure 2.4.3. Comparison of the risk ratio of serious adverse events between cannabinoid and control groups.



eFigure 2.4.4. Comparison of the risk ratio of withdrawals from trials due to adverse events between cannabinoid and control groups.



eFigure 2.4.5. Funnel plot of standard error against the RR of adverse events in children with cannabinoid compared with control.



eFigure 2.4.6. Funnel plot of standard error against the RR of serious adverse events in children with cannabinoid compared with control.

2.4.14.2 eTables

eTable 2.4.1. Comparison of the risk of serious adverse events between cannabinoid and control groups.

Serious adverse events	Trials	Cannabinoids (e/n)	Control (e/n)	Risk ratio	I^2	Confidence Interval
Acute respiratory failure	2	2/234	0/161	2.14	0%	0.22-20.40
Elevation in transaminase levels	4	22/370	2/206	2.19	40%	0.39-12.19
Elevation in ALT	3	9/383	0/237	4.22	0%	0.75-23.75
Elevation in AST	3	10/383	0/237	4.80	0%	0.88-26.29
Pneumonia	2	5/234	2/161	1.80	0%	0.35-9.23
Rash	2	4/176	2/82	0.65	20%	0.10-4.42
Status epilepticus	5	8/577	5/361	1.08	0%	0.38-3.07

eTable 2.4.2. Comparison of the risk of adverse events based on organ system between cannabinoid and the control groups.

Adverse event	Trials	Cannabinoids (e/n)	Control (e/n)	Risk ratio	I^2	Confidence Interval
GI-related AEs						
Abdominal pain	4	16/176	0/119	2.31	0%	0.77-6.92
Constipation	6	23/493	13/289	1.10	0%	0.57-2.11
Decrease in appetite	13	299/1132	142/718	1.61	62%	1.08-2.41
Increase in appetite	7	54/443	64/348	1.07	72%	0.33-3.41
Diarrhea	10	245/1155	76/710	1.82	35%	1.30-2.54
Drooling	2	4/90	0/89	4.54	0%	0.57-36.16
Dry mouth	4	113/409	43/314	2.40	0%	1.85-3.10
Gastroenteritis	3	12/183	6/134	0.86	69%	0.11-6.87
Retching	2	9/133	0/110	6.95	0%	0.90-53.65
Vomiting	9	114/954	54/619	1.31	19%	0.89-1.93
CNS-related AEs						
Anxiety	4	52/395	24/301	1.04	63%	0.29-3.76
Convulsion	2	8/88	5/66	0.63	78%	0.04-10.20
Decrease in concentration	2	89/301	34/207	1.80	91%	0.54-5.96
Depression	2	24/128	30/128	0.79	0%	0.49-1.27
Dizziness	5	116/389	43/302	2.57	51%	1.13-5.86
Headache	4	23/308	29/220	0.65	0%	0.39-1.07
Insomnia	2	15/145	4/108	1.96	0%	0.65-5.90
Mood changes	5	83/363	61/269	0.94	0%	0.70-1.27
Nervousness	2	5/63	0/27	3.27	0%	0.42-25.45
Restlessness	5	57/344	37/256	0.95	0%	0.66-1.37
Sedation	3	23/128	2/107	4.78	0%	1.42-16.07
Seizures	6	43/1046	16/774	1.57	0%	0.89-2.77
Euphoria	6	114/459	21/365	4.89	65%	1.93-12.35

Somnolence	14	390/1239	127/825	2.28	8%	1.83-2.85
Status epilepticus	4	27/429	16/295	0.99	0%	0.54-1.81
Tics	2	4/192	2/98	1.09	0%	0.24-4.95
Psychomotor hyperactivity	2	1/63	2/43	0.29	0%	0.04-2.19
Eye-related AEs						
Blurred vision	2	72/301	14/207	4.85	0%	2.92-8.03
Respiratory system-related AEs						
Cough	3	19/343	7/263	1.59	0%	0.70-3.65
Lower RTI	5	43/518	33/472	1.13	0%	0.74-1.72
Nasopharyngitis	8	67/727	442/38	1	0%	0.68-1.47
Nose congestion	2	7/90	3/89	1.51	48%	0.17-13.55
Streptococcal pharyngitis	2	4/136	3/111	0.90	0%	0.21-3.95
Respiratory distress	3	13/544	9/540	1.36	0%	0.59-3.14
Upper RTI	8	73/686	47/453	0.94	0%	0.65-1.36
Biochemical investigation-related AEs						
Increase in AST	5	43/544	1/308	5.69	0%	1.74-18.64
Increase in ALT	6	60/605	3/367	5.67	0%	2.23-14.39
Increase in GGT	2	25/234	2/161	4.70	63%	0.33-67.17
Circulatory system-related AEs						
Hypotension	3	77/145	84/152	0.83	66%	0.31-2.24
Tachycardia	3	23/229	24/235	0.99	0%	0.59-1.65
Skin-related-AEs						
Rash	3	12/222	5/194	1.88	0%	0.70-5.02
Death	3	4/304	6/216	0.73	0%	0.23-2.23
General AEs						
Fatigue	8	138/776	43/463	1.67	25%	1.22-2.30
Hypersensitivity	2	2/116	1/122	1.79	0%	0.22-14.21
Lethargy	3	68/335	20/238	1.81	0%	1.16-2.83
Pyrexia	11	181/1012	103/685	1.22	43%	0.92-1.63
Sepsis	2	13/358	23/355	0.60	0%	0.31-1.15
Viral Infection	2	4/113	1/92	1.25	62%	0.05-31.21

eTable 2.4.3. Comparison of adverse events reported by one trials based on organ system between cannabinoid and control groups.

Study	Adverse event	Cannabinoids	Control
GI related-AEs			
Freeman et al, 2020	Bloating	3/59	0/23
Thiele et al, 2018	Nausea	4/86	3/85
Thiele et al, 2018	Aphthous stomatitis	1/86	0/85
Thiele et al, 2018	Faeces soft	1/86	0/85
Thiele et al, 2018	Haemorrhoids	1/86	0/85
Thiele et al, 2018	Steatorrhea	1/86	0/85
Thiele et al, 2018	Teething	1/86	0/85

Thiele et al, 2018	Abdominal discomfort	0/86	1/85
Thiele et al, 2018	Dysphagia	0/86	1/85
Thiele et al, 2018	Faeces discoloured	0/86	1/85
Thiele et al, 2018	Gastro-oesophageal reflux disease	0/86	1/85
Thiele et al, 2018	Tongue disorder	0/86	1/85
Metabolism and nutrition disorder-related AEs			
Knoller et al, 2002	Hyperglycemia	7/30	6/37
General disorder-related AEs			
Thiele et al, 2018	Crying	1/86	0/85
Thiele et al, 2018	Feeling drunk	1/86	0/85
Thiele et al, 2018	Influenza like illness	1/86	0/85
Thiele et al, 2018	Oedema peripheral	1/86	0/85
Thiele et al, 2018	Discomfort	0/86	1/85
Thiele et al, 2018	Gait disturbance	0/86	1/85
Aran et al, 2021	Weight loss	23/188	3/94
Maas et al, 2005	Gastrointestinal and hepatobiliary disorders	6/428	9/418
Berry-Kravis et al, 2022	Application site pain	7/109	1/102
Central nervous system-related AEs			
Efron D et al, 2020	Eyes rolled up	1/4	0/4
Efron D et al, 2021	Tics	1/4	0/4
Efron D et al, 2021	Ear ringing	1/4	0/4
Fairhurst et al, 2020	Poor quality sleep	3/47	1/25
Thiele et al, 2018	Hypotonia	2/86	2/85
Thiele et al, 2018	Aggression	3/86	1/85
Thiele et al, 2018	Sleep disorder	2/86	2/85
Thiele et al, 2018	Irritability	2/86	1/85
Devinsky et al, 2018 a	Ataxia	3/27	0/7
Devinsky et al, 2018 a	Abnormal behaviour	1/27	1/7
Freeman et al, 2020	Claustrophobia	1/59	0/23
Chang et al, 1979	Paranoia	1/15	0/15
Dalzel et al, 1989	Heavy eyes	2/22	1./22
Aran et al, 2021	Hallucinations	9/188	5/94
Chan et al, 1987	Muscle twitching	2/36	1/36
Respiratory system-related AEs			
Thiele et al, 2018	Acute respiratory failure	3/86	0/85
Thiele et al, 2018	Wheezing	2/86	0/85
Berry-Kravis et al, 2022	Rhinorrhea	2/109	2/102
Berry-Kravis et al, 2022	Pharyngitis streptococcal	3/109	2/102
Thiele et al, 2018	Bronchitis	4/86	1/85
Infections-related AEs			
Thiele et al, 2018	Urinary tract infection	2/86	2/85

Thiele et al, 2018	Ear infection	2/86	2/85
Freeman et al, 2020	Tonsilitis	1/59	0/23
	Injury poisoning-related AEs		
Thiele et al, 2018	Fall	2/86	2/85
Thiele et al, 2018	Head injury	1/86	1/85
Thiele et al, 2018	Contusion	1/86	0/85
Thiele et al, 2018	Hand fracture	1/86	0/85
Thiele et al, 2018	Limb injury	1/86	0/85
Thiele et al, 2018	Tooth fracture	1/86	0/85
	Skin-related AEs		
Efron D et al, 2020	Acne	1/4	0/4
Dalzel et al, 1989	Pruritis	1/22	1/22
Berry-Kravis et al, 2022	Skin abrasion	1/109	1/102
	Renal and urinary system-related AEs		
Efron D et al, 2020	Urinary incontinence	1/4	0/4
Efron D et al, 2020	Urinary retention	4/86	0/85
	Hepatobiliary disorders-related AEs		
Thiele et al, 2021	Acute hepatic failure	1/86	0/85
Thiele et al, 2021	Hepatic toxicity	1/86	0/85
	Investigations-related AEs		
Thiele et al, 2018	Weight decreased	2/86	2/85
Thiele et al, 2018	Increase in prolactin levels	1/86	0/85
Thiele et al, 2018	Decrease in oxygen saturation	1/86	1/85
Thiele et al, 2018	Weight increased	1/86	1/85
Thiele et al, 2018	Drug levels increased	1/86	0/85
Thiele et al, 2018	Respiratory rate increased	1/86	0/85
Thiele et al, 2018	Temperature difference of extremities	1/86	1/85
Thiele et al, 2018	Urine output	1/86	0/85
	Cardiovascular system-related AEs		
Thiele et al, 2018	Arrhythmia	1/86	1/85
Knoller et al, 2002	Hypertension	7/30	6/37
Maas et al, 2005	Cardiac disorder	11/428	5/418
Maas et al, 2005	Endocrine disorder	5/428	5/418
	Blood and lymphatic system-related AEs		
Thiele et al, 2018	Leukopenia	1/86	2/85
Thiele et al, 2018	Leukocytosis	1/86	0/85
Thiele et al, 2018	Thrombocytopenia	1/86	0/85
Knoller et al, 2002	Anemia	8/15	21/37
Knoller et al, 2002	Hypokalemia	10/30	15/37
Maas et al, 2005	Blood and lymphatic system disorder	7/428	7/418

Ear labyrinth-related AEs			
Thiele et al, 2018	Ear pain	0/86	0/852
Eye-related AEs			
Thiele et al, 2018	Retinal disorder	0/86	1/85
Chan et al, 1987	Ocular swelling	1/12	0/36
Serious adverse events			
GI-related AEs			
Fairhurst et al, 2020	Food aversion and retching	1/47	0/25
Respiratory system-related AEs			
Fairhurst et al, 2020	Respiratory tract infection	1/47	1/25
CNS-related AEs			
Fairhurst et al, 2020	Change in seizure profile	2/47	1/25
Fairhurst et al, 2020	Shunt malfunction	0/47	1/25
Aran et al, 2021	Seizures	3/188	0/94
Aran et al, 2021	Suicide attempt	1/188	0/94
Aran et al, 2021	Arteriovenous malformation	0/188	1/94
Other AEs			
Aran et al, 2021	Broken leg	1/188	0/94

2.4.15 Search strategy

2.4.15.1 Multifile Ovid Search

Embase <1974 to 2021 June 16>
Ovid MEDLINE(R) ALL <1946 to June 16, 2021>
APA PsycInfo <1806 to June Week 1 2021>

1 Cannabis/

2 exp Cannabinoids/

3 Cannabaceae/

4 Medical Marijuana/

5 Marijuana Use/

6 Marijuana Smoking/

7 cannab*.tw, kf.

8 Mari?uana*.tw, kf.

9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw, kf.

10 (19GBJ60SN5 or 2N4O9L084N or 7J8897W37S or K4H93P747O).rn.

11 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw, kf.

12 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw, kf.

13 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw, kf.

14 or/1-13 [CANNABIS CONCEPT]

15 exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. [CHILDREN CONCEPT]

16 14 and 15

17 exp Animals/ not (exp Animals/ and Humans/)

18 16 not 17 [EXCLUDING ANIMAL ONLY STUDIES]

19 (202106* or 202107* or 202108* or 202109* or 20211* or 2022*). dt, ez, da.

20 18 and 19

21 20 use medall

22 cannabis/

23 exp cannabinoid/

24 cannabaceae/

25 exp "cannabis (genus)"/

26 medical cannabis/

27 exp "cannabis use"/

28 cannab*.tw, kw.

29 Mari?uana*.tw, kw.

30 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw, kw.

31 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw, kw.

32 (8063-14-7 or 1972-08-3 or 13956-29-1 or 51022-71-0 or 8001-54-5 or 33086-25-8 or 36557-05-8 or 24359-49-7).rn.

33 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw, kw.

34 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw, kw.

35 or/22-34

36 exp child/ or exp newborn disease/ or exp infant/ or exp adolescent/ or exp pediatrics/ or abandoned child/ or gifted child/ or orphaned child/ or unwanted child/ or "minor (person)"/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

37 35 and 36

38 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

39 Animal experiment/ not (human experiment/ or human/)

40 38 or 39

41 37 not 40

42 limit 41 to dc=20210617-20220427

43 42 use oemezd

44 exp cannabis/

45 exp cannabinoids/

46 marijuanas/

47 marijuana usage/

48 marijuana legalization/

49 cannab*.tw.

50 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw.

51 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw.

52 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw.

53 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw.

54 or/44-53 [Cannabis Concept]

55 limit 54 to (childhood <birth to 12 years> or adolescence <13 to 17 years>)

56 exp pediatrics/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

57 54 and 56

58 55 or 57

59 exp Animals/ not (exp Animals/ and Humans/)

60 58 not 59

61 60 use psyc17

62 60 use psyc18

63 60 use psyc16

64 or/61-63

65 21 or 43 or 64

66 remove duplicates from 66

**Note Ovid multifile search of MEDLINE, Embase, and PsycInfo were run on June 20, 2020, June 17, 2021, April 27, 2022, April 24, 2023, and March 1, 2024. The search remains unchanged except for date limits.*

2.4.15.2 Cochrane Library (Wiley) Search Strategy

ID Search

#1 MeSH descriptor [Cannabis] this term only

#2 MeSH descriptor [Cannabinoids] explode all trees

#3 MeSH descriptor [Cannabaceae] this term only

#4 MeSH descriptor [Medical Marijuana] this term only

#5 MeSH descriptor [Marijuana Use] explode all trees

#6 MeSH descriptor [Marijuana Smoking] this term only

#7 cannab* ti, ab, kw

#8 Mari? uana* ti, ab, kw

#9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla) ti, ab, kw

#10 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex) ti, ab, kw

#11 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726") ti, ab, kw

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 MeSH descriptor [Child] explode all trees

#14 MeSH descriptor [Congenital, Hereditary, and Neonatal Diseases and Abnormalities] explode all trees

#15 MeSH descriptor [Infant] explode all trees

#16 MeSH descriptor [Adolescent] this term only

#17 MeSH descriptor [Pediatrics] explode all trees

#18 MeSH descriptor [Child, Abandoned] this term only

#19 MeSH descriptor [Child, Exceptional] this term only

#20 MeSH descriptor [Child, Orphaned] this term only

#21 MeSH descriptor [Child, Unwanted] this term only

#22 MeSH descriptor [Minors] this term only

#23 (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or "premature birth*" or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or "elementary school*" or "nursery school*" or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*)ti, ab, kw

#24 (child* or adolesc* or pediat* or paediat*)so

#25 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

**Note Cochrane Library search via Wiley were run on June 20, 2020, June 17, 2021, April 27, 2022, April 24, 2023, and March 1, 2024. The search remained unchanged except for date limits and a correction in a typo between June 2020 and June 2021 in Line #11 where ti, ab, kw was used instead of ti, ab, kw*

Chapter 3 Real-world safety of cannabidiol and its clinical drug interactions in children and adolescents Insights from pharmacovigilance study and systematic literature review

3.1 Overview

In the identified studies during evidence synthesis, CBD was the most common cannabinoid used in children for multiple indications, including drug-resistant epilepsies, autism, and symptom management in children with cancer. Real-world evidence on the safety profile of CBD in children is sparse. Additionally, in section 2.4, CBD was associated with an increased risk of adverse events in children. Most of the adverse events were due to underlying CBD-related drug interactions.

In this chapter, we analyzed the US Food and Drug Administration Adverse Event Reporting System (FAERS) and EudraVigilance databases to review CBD-related adverse events (pharmacovigilance reports). Second, we synthesized evidence on CBD-related clinical drug interactions in children reported by studies identified in the living systematic review. We also performed a disproportionality analysis of commonly reported suspected adverse events with CBD.

Our study provides prospective research questions to determine the causal relationship between CBD and suspected adverse events and research questions to study CBD-related drug interactions in children.

Real-world safety of cannabidiol and its clinical drug interactions in children and adolescents Insights from pharmacovigilance study and systematic literature review

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Manuscript status

Ready for journal submission.

3.2 Abstract

Background With increasing use of Cannabidiol (CBD) for medical purposes, very little is known about its real-world safety and clinical drug interactions in children. We aimed to study the real-world safety profile of CBD in children using open pharmacovigilance databases and systematically review literature on CBD-related clinical drug interactions in children.

Method We analyzed the US Food and Drug Administration Adverse Event Reporting System (FAERS) and EudraVigilance databases to review CBD-related spontaneous reports in children. A descriptive analysis of spontaneous reports from both data sources was conducted, followed by a disproportionality analysis of FAERS data to generate signals using OpenVigil 2.1. MEDLINE, Embase, PsycInfo (via Ovid), and the Cochrane Library were searched from inception to March 2024 to identify literature on CBD-related clinical drug interactions in children. Two reviewers independently performed screening, data extraction, and quality assessment.

Result Two-thousand sixty-eight CBD-related spontaneous reports from FAERS (n=274; 13.25%) and EudraVigilance (n=1794; 86.75%) were identified. Central nervous system-, gastrointestinal-, and respiratory-related were the most reported suspected adverse events (AEs). Strong signals were detected for hospitalization [Proportional Reporting Ratio (PRR) 30.83 (26.03-36.51), 127 reports], sudden unexplained death in epilepsy [PRR 27.64 (95% CI 10.06-75.91), 4 reports], seizures [PRR 19.77 (95% CI 18.03-21.66), 328 reports] and death [PRR 14.07 (12.27-16.13), 176 reports]. Of 19 included studies, 13 (68.4%) included children exclusively (n=267 children). A total of 14 CBD-related clinical drug interactions were reported in children. CBD was commonly reported to interact with clobazam (n=8/19, 42.10%), valproic

acid (n=4/19, 21.05%), mTOR inhibitors (everolimus and sirolimus; n=3/19, 15.78%), topiramate (n=2/19, 10.50%), and zonisamide (n=2/19, 10.50%).

Conclusion Our analysis highlights need to monitor CNS-related suspected AEs in children using CBD. Since CBD is reported to interact with multiple medications, there is a need for cautious monitoring of CBD in children on multiple medications.

Keywords Safety; real-world evidence; drug-resistant epilepsy; cannabidiol; drug interaction; pharmacovigilance; children

3.3 Introduction

Due to its nonintoxicating proprieties and widespread anecdotal claims of benefit, Cannabidiol (CBD) is one of the most widely studied active components of the cannabis plant.(1) CBD can either be derived from plants of the genus *Cannabis* or manufactured in the laboratory.(2) Phytocannabinoids or plant-based CBD products (also called CBD-enriched cannabis herbal extracts) are available in many forms with varying components, including CBD tetrahydrocannabinol (THC) ratios and formulations, including oils, sprays, and gels.(3)

Purified CBD (Epidiolex®) has marketing authorization in children (≥1 or 2 years of age, depending on jurisdiction) with refractory epilepsies owing to its promising effects showing a reduction in seizure frequency.(4) In randomized controlled trials (RCTs), CBD has been well-tolerated in children with refractory epilepsies (including Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex).(5, 6) However, CBD is reported to be involved in many biological pathways and is known to interact with drug metabolism enzymes, thus affecting the activity of other therapeutic entities, including medications.(7) Children with refractory epilepsy and other complex health illnesses such as autism spectrum disorder (ASD), cancer, and pain may be taking multiple medications.(9) The addition of CBD in these children may increase the risk of drug interactions and AEs.(10) There is a need to generate evidence on the safety of CBD and its drug interactions in children with complex health illnesses to inform clinical practice.

The use of CBD may cause adverse events in children due to its multiple pharmacological targets and ability to affect drug metabolism.(11) In RCTs, children receiving CBD reported AEs involving multiple physiological systems, including somnolence, diarrhea, decreased appetite, and increased serum liver transaminase.(5, 6) Epidiolex is not available in all regions of the world nor reimbursed for most families or indications, leading parents of children with complex health illnesses often accessing CBD products from the recreational markets.[12] Considering the widespread use of CBD, there is a need to collect evidence related to its safety profile in children.

To our knowledge, no study has reported a synthesis of spontaneously reported CBD-related AEs. Therefore, we aimed to study the real-world safety profile of CBD in children by reviewing spontaneous AE reports from publicly available databases (US Food and Drug Administration Adverse Event Reporting System (FAERS) and EudraVigilance) and systematically review literature reporting on CBD-related clinical drug interactions in children.

3.4 Methods

3.4.1 Safety profile of CBD in the real-world

Two large open pharmacovigilance databases, EudraVigilance and FAERS, were reviewed for CBD-related spontaneous pharmacovigilance reports. CBD approved by several drug regulating agencies, including the United States Food and Drug Administration (US FDA), European Medical Agency (EMA), Australian Therapeutics and Goods Administration (TGA), and recently Health Canada, following clinical trials supporting its safety and efficacy is referred as **regulated CBD**.(13) In contrast, CBD products without any regulatory body approval, including cannabis herbal extracts, are referred as **unregulated CBD**.(14)

3.4.1.1 Data sources

FAERS(15) and EudraVigilance(16) databases were explored to review CBD-related spontaneous reports in children and adolescents aged 18 years or below, irrespective of indication. European Medical Agencies govern the EudraVigilance database on behalf of the European Union Medicines Regulatory Network.(16, 17) It collects spontaneous reports of suspected adverse events (AEs) from health care professionals (HCPs) and non-HCPs in the European Economic Area (EEA) and non-EEA.(17) EudraVigilance reports data on age groups, sex, AEs, source of reporting, indication, suspect/interacting drugs, and concomitant drugs in spontaneous reports. FAERS is the world's largest pharmacovigilance database, maintained by the FDA, and is used for pharmacovigilance data collection, mining, and signal detection.(15, 18)

FAERS receives spontaneous reports of pharmaceutical products regulated in the US from all over the world. However, most reports are domestic and submitted by manufacturers due to regulatory obligations. FAERS reports the following information in spontaneous reports age, sex, reporter type, report source, adverse event suspected active ingredients, indication, seriousness, outcomes, concomitant products, and country.(15) In FAERS, serious AE means AE leading to any of these outcomes death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly, or birth defect.(19)

3.4.1.2 Data cleaning and mining

CBD-related spontaneous reports from the FAERS and EudraVigilance public dashboard were downloaded from inception to March 2024. Microsoft Excel files from both data sources were cleaned separately with the help of R studio (024.04. 1+748.pro2.) using R programming. Spontaneous reports were deduplicated based on the EU Local Number (EudraVigilance), case

ID (FAERS), age, sex, Medical Dictionary for Regulatory Activities (MedDRA) preferred AE terms, and drugs. Unregulated CBD data were duplicated based on EU local numbers to avoid regulated CBD duplicates. Data were cleaned extensively to separate indications, AEs, suspect/interacting drugs, outcomes, and outcomes separately in their respective columns represented by their respective case IDs. In the FAERS, we included spontaneous reports of patients aged 18 years or below. EudraVigilance reports age groups; we included spontaneous reports with an age group from 2 months-2 years to 12-17 years. EudraVigilance database does not data on exact age, but by age brackets. Spontaneous reports with an age/age group >18 years or those not specifying an age/age group were excluded. R scripts used to clean and analyze the data can be accessed openly on the Open Science Framework.

3.4.1.3 Statistical analysis

Descriptive analysis was performed for categorical variables as numbers and proportions and numerical variables as means with SD or medians with ranges. Commonly suspected MedDRA preferred AE terms data from all data sources were visualized using a heatmap plot. All analyses were conducted in R studio.

3.4.1.4 Signal detection

A Disproportionality analysis was conducted to establish an association between AEs and CBD.(15) Disproportionality analysis utilizes a contingency table (2 × 2 table) to compare the frequency of AE with specific medication against the frequency of the same AE reported with all other medications in the database.(20) A signal is identified when an AE of interest is reported more frequently with a suspected drug than all other medications.(15, 20) **eTable 3.1.** represents the contingency table (2 × 2) and the formula to calculate the proportional reporting ratio (PRR) and reporting odds ratio (ROR). PRR and ROR are displayed with 95% confidence intervals

computed with chi-square with Yates' correction. A signal is confirmed if PRR is ≥ 2, chi-square≥ 4, number of cases ≥ 3, and 95% CI of ROR is ≥1.(21) Signal detection was performed using OpenVigil 2.1-MedDRA-v24.(22) OpenVigil is an open-source tool for mining and analyzing pharmacovigilance data available from FAERS.(22, 23) Disproportionality analysis was conducted for AEs where CBD was reported as the primary suspect and restricted to children and adolescent reports only; we selected the advance search option and restricted our search based on ages 0-18 years. Disproportionality analysis included the analysis of spontaneous reports for both regulated and unregulated CBD. It was performed in March 2024 and updated in August 2024. OpenVigil included data from Q4/2003-Q2/2024 from FAERS.

3.4.2 CBD-related drug interactions systematic review

The systematic review protocol was registered with PROSPERO (CRD42020187433). The systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA),(24) PRISMA-S guidelines,(25) and Cochrane collaboration guidelines.(26) This is a secondary analysis from the living systematic review published elsewhere (under peer-review). **Appendix A** provides the complete methodology of the systematic review.

3.5 Results

3.5.1 Safety profile of CBD in the real-world

3.5.1.1 Characteristics of included ICSRs and children

A total of 2,068 spontaneous reports (274 from FAERS, 104 from regulated EudraVigilance CBD, and 1690 from unregulated EudraVigilance CBD) reporting suspected AEs in children on CBD were identified. Healthcare professionals were the primary sources of spontaneous reports in FAERS (n=165/274, 60%) and EudraVigilance (regulated, n=89/104,

86%; unregulated, 1661/1690, 98%). Most of the included reports in FAERS were from the US (n=199/274, 73%). In EudraVigilance, they were from European economic areas (n=84/104, 81%) for regulated CBD and non-European-economic areas (n=1603/1690, 95%) for unregulated CBD. In FAERS, the median age of children was 9 (range 0.5-18) years. EudraVigilance reported data on age groups only; majority of children were aged 3–11 years (regulated, n=62/104, 60%; unregulated, 914/1690, 54%), and in the FAERS, the majority were from 6-11 years (n=96/274, 35%) and 12-18 years (n=101/274, 36.9%). Most common indication reported for CBD was epilepsy in FAERS (n=132/274, 48.2%) and Lennox-Gastaut syndrome (regulated, n=36/104, 34.6%; unregulated, 613/1690, 44%) in EudraVigilance. **Tables 3.1. and 3.2.** report the complete characteristics of spontaneous reports that included children and adolescents in the reports.

3.5.1.2 Characteristics of included Suspected AEs

In EudraVigilance reports, CBD was reported as suspect for all AEs except for a few reports, where it was reported to interact with other drugs (regulated CBD, n=5/104, 4.8%; unregulated CBD, 26/1690, 1.5%). In FAERS, serious AEs were reported in four-fifths (n=213/274, 77.7%) of the reports, and children were hospitalized in over two-fifths (n=114/274, 42%) reports. EudraVigilance reports data on outcomes of suspected AEs; outcomes for 52.5% (n=136) of suspected AEs in regulated CBD and 60% (n=2360) of suspected AEs in unregulated CBD were unknown, followed by recovered/resolved for 28.2% (n=73) of AEs in regulated CBD and 16% (n=619) of AEs in unregulated CBD. Median (range) suspect, concomitant, and total medications were 1 (1-20), 1 (1-16), and 2 (2-21), respectively, in FAERS. In EudraVigilance, median (range) suspect, concomitant, and total medications were 1 (1-9), 1 (0-7), and 2.5 (1-10), respectively, for regulated CBD. In unregulated CBD, median (range) suspect, concomitant, and

total medications were 1 (0-24), 0 (0-36), and 1 (0-37), respectively. Clobazam (CLB), valproic acid (VPA), levetiracetam (LEV), vigabatrin, and lamotrigine were the most common suspect and concomitant medications, along with CBD, in identified reports. **eTable 3.2.** provides a comprehensive list of commonly suspected and concomitant medications with CBD in the identified spontaneous reports.

Seizure, somnolence, hypersomnia, abnormal behavior, aggression, agitation, asthenia, and falls were the common central nervous system (CNS)-related suspected AEs with CBD. Off-label use, drug ineffectiveness, drug interaction, prescribed overdose, incorrect dose administered, and product supply issues were the most reported suspected AEs from medication errors or product-related suspected AEs (MedDRA system organ classification). **Figure 3.1.** shows commonly reported suspected AEs in our identified reports. In gastro-intestinal-related suspected AEs, vomiting, decrease in appetite, diarrhea, constipation, abdominal pain, and constipation were top six most frequently reported. Fatigue, lethargy, fever, and weight loss were frequently reported as general suspected AEs. Pneumonia, decrease in oxygen saturation, and nasopharyngitis were common respiratory system-related suspected AEs. Viral Infections were also frequently reported. Other commonly reported suspected AEs include an increase in liver transaminase levels (both alanine and aspartate transaminase) and an increase in plasma concentration of antiepileptic and antipsychotic medications. Supplementary **eTable 3.1.** provides a comprehensive list of suspected AEs reported in CBD-related spontaneous reports.

3.5.1.3 Disproportionality analysis

Signals were detected where CBD was reported as the primary suspect for suspected AEs sudden unexplained death in epilepsy, status epilepticus, fall, head injury, sedation, behavior disorder, decreased appetite, decreased weight, death, hospitalization, pneumonia, aspiration,

viral infection, and rhinovirus infection. **Table 3.3.** tabulates the positive signals for AEs associated with CBD as a primary suspect. Signals were strong for seizures [PRR 19.767 (95% CI 18.03-21.66), 328 reports], sudden unexplained death in epilepsy [PRR 27.64 (95% CI 10.06-75.91), 4 reports], death [PRR 30.83 (26.03-36.51), 176 reports], and hospitalization [PRR 30.83 (26.03-36.51)]. **eTable 3.4.** provides a list of AEs with CBD as a primary suspect with negative signals.

3.5.2 CBD-related DDIs systematic review

Nineteen studies reporting CBD-related clinical drug interactions in children were included. Of the 19 included studies (546 children and adults),(27-45) 68.4% (n=13/19) included children exclusively (267 children)(27-30, 32, 33, 35-40, 45) and 15.7% (n=3/19) of studies were multicentric.(40, 41, 45) A total of 14 CBD-related drug interactions were reported in the included studies; (27-45) all interactions were pharmacokinetic, except one study reported a pharmacodynamic interaction.(37) **eTable 3.5.** presents the complete characteristics of the included studies and their participants. **Appendix A** provides the complete results of a systematic review.

CBD was reported to interact with clobazam (n=8/19, 42.10%), (33, 35-37, 40, 42, 43, 45) valproic acid (n=4/19, 21.05), (28, 36, 37, 41) mTOR inhibitors (everolimus and sirolimus; n=3/19, 15.79%),(30, 38, 44) topiramate (n=2/19, 10.5%),(36, 43) zonisamide (n=2/19, 10.5%),(39, 43) methadone (n=1/19, 5.2%),(27) lithium (n=1/19, 5.2%),(29) brivaracetam (n=1/19, 5.2%),(34) fluoxetine (n=1/19, 5.2%),(31) levothyroxine (n=1/19, 5.2%),(32) levetiracetam (n=1/19, 5.2%),(39) stiripentol (n=1/19, 5.2%),(41) rufinamide (n=1/19, 5.2%),(43) and eslicarbazepine (n=1/19, 5.2%).(43) CBD and valproic acid co-administration resulted in the elevation of liver function tests and caused thrombocytopenia. Nine of 23

(39.13%) children co-administered CBD with valproic acid experienced thrombocytopenia.(37) Clobazam, zonisamide, levetiracetam, and levothyroxine increased the plasma levels of CBD. One study reported a bidirectional drug interaction between Clobazam and CBD, leading to increased plasma levels of both n-clobazam (an active metabolite of Clobazam) and CBD.(40) Levothyroxine increased plasma levels of CBD in a case series of 12 patients.(32) **Table 3.4.** provides a comprehensive summary of CBD-related clinical drug interactions.

3.6 Discussion

This is the first study to report on the safety profile of CBD (regulated and unregulated) during medical use in children using data from large pharmacovigilance databases (FAERS and EudraVigilance) and its clinical drug interactions from literature in children. Commonly identified spontaneous reports were CNS-, gastrointestinal-, general-, and respiratory system-related suspected AEs. Frequently reported CNS-related suspected AEs include seizure, somnolence, hypersomnia, abnormal behavior, aggression, agitation, and asthenia. Seizures, sudden unexplained death in epilepsy, falls, decreased appetite, death, hospitalization, pneumonia, and aspiration were the positive signals (proportional reporting ratio is ≥ 2, chi-square≥ 4, number of cases ≥ 3, and 95% CI of reporting odds ratio is ≥1) for CBD compared to other drugs in the FAERS database. In the systematic review, CBD is reported to interact with co-administered other medications such as valproic acid, levetiracetam, clobazam, stiripentol, and brivaracetam. CBD-related drug interactions are linked to negative effects associated with its use in children; further drug interaction may impact the efficacy of administered drugs, including CBD.

CBD has garnered much attention for the management of seizures in children with DRE who are non-responsive to first-line antiepileptic medications.(46) Among the identified

spontaneous FAERS reports citing seizure as the common indication, 77% reported serious suspected AEs, and 42% reported hospitalization as an outcome of suspected AEs. This highlights the urgent need to monitor and minimize the risk of AEs in children receiving CBD. Healthcare professionals should be aware of the risk of AEs with CBD. CBD information leaflets should be updated with clear labeling instructions for potential AEs in children. Healthcare providers should discuss the risks of AEs with parents interested in CBD as a treatment option for their children. Spontaneous reports from EudraVigilance lack data on the seriousness of suspected AEs. CBD was reported as suspected in 95% of regulated CBD reports and 98.5% of unregulated reports, with an unknown outcome in spontaneous reports from EudraVigilance. CBD product-related AEs (off-label use, drug ineffectiveness, drug interaction, and inadequate quality of CBD products) were also reported in a higher proportion in the included reports. Quality issues and medication errors related to (unlicensed) CBD products were reported. Parents often access cannabis products available from recreational markets.(12, 47) Unlicensed CBD products may not have the same concentration of CBD as claimed on the labels of formulations, and the USFDA has issued a warning letter to industries on CBD products to protect the public.(48) Additionally, unlicensed CBD products have potential to contain tetrahydrocannabinol.(49) In a case series study of 105 CBD products, 58% of CBD products were over-labeled, and THC was present in 35% of CBD products.(49)

Epilepsy was the main reported indication for CBD use in children in the identified reports. In Europe, CBD has orphan drug status (used for rare diseases) and is approved as an adjunct therapy with Clobazam in children with Lennox-Gastaut syndrome, Dravet syndrome, and Tuberous Sclerosis Complex.(50) Four randomized controlled trials examined the therapeutic efficacy of CBD in controlling treatment-resistant seizures when used with clobazam,

they reported synergistic effects of interaction for seizure reduction.(51) However, risks of somnolence and sedation were commonly reported with co-administration of CBD and clobazam.(51) In the included spontaneous reports, seizures were reported in a higher proportion as suspected AEs with CBD. In over 60% of the identified spontaneous reports, CBD was used without clobazam with seizure as an indication, and seizures were reported as suspected AEs. Uncontrolled seizures with CBD are a concern, and the literature reports uncontrolled seizures in children when CBD used without clobazam.(51, 52) Further, this can be linked to confounding by indication, potential presence of THC, and lack of medical oversights. Uncontrolled seizures can be linked to hospitalization, sudden unexplained death in epilepsy, and death in children, and we identified strong signals for them. Further, uncontrolled seizures can be linked to increased risk of falls and injuries; we also identified positive signals for falls and head injuries with CBD as a primary suspect. Additionally, falls and injuries may be due to somnolence or sedation, which were reported with CBD use as suspected AEs in the identified reports. CBD has been reported to decrease the immune cell count in preclinical studies,(53) which may be further linked to an increased risk of infections. In our meta-analysis published elsewhere, CBD was not associated with a significant risk of infections in children.(6) Pneumonia, viral infections, and rhinovirus infections were reported in higher proportions, with positive signals associated with CBD as the primary suspect in our current analysis. We also noted a positive signal for decreased appetite, which can be correlated with weight loss. CBD acts as an inverse agonist of the CB1 receptor and suppresses the hyperphagic action of endogenous cannabinoids.(54)

Children received CBD along with other suspected and concomitant medications in identified spontaneous reports. The negative effects, such as elevation in liver transaminase levels, somnolence, lethargy, and fatigue associated with CBD use, are attributed to its

interaction with co-administered drugs in children. (27-30, 32, 33, 35-40, 45) In our included studies, CBD was reported to inhibit cytochrome (CYP) p450 enzymes; CYP 3A4, 2D6, 2C9, and 2C19 and uridine diphosphate-glucuronosyltransferase (UGT) 1A9, 2B4, 1A6, and 2B7. CBD inhibits renal clearance of lithium and increases its plasma concentration.(29) CBD and Clobazam drug interaction has been well studied in children, reported by eight included studies.(28, 36, 37, 41) CBD increases plasma levels of n-clobazam by 3-4 times; one study reported bidirectional interaction between CBD and clobazam with an increase in both CBD and n-clobazam levels.(40) CBD and clobazam drug interaction does not have any impact on therapeutic effectiveness (47), but there is an increased risk of CNS-related AEs such as somnolence, lethargy, and fatigue(48); we reported positive signals for sedation in our analysis. In a single-arm study, 21.8% of children receiving CBD with clobazam reported somnolence.(55) CBD and valproic acid interaction resulted in thrombocytopenia and elevation in liver transaminase levels in the retrospective chart review included in this systematic review.(37) This warrants monitoring platelets and liver function tests in children receiving CBD and valproate. In a case report, CBD increased the plasma levels of fluoxetine in a adolescent with a null CYP 2D6 variant.(31) Individual responses to CBD vary in terms of the safety, benefits, and pharmacokinetics of CBD and co-administered drugs. The safety of CBD in patients with genetic polymorphisms needs to be studied extensively. Off-label use of CBD was commonly reported in spontaneous reports. Off-label use increases the risk of developing AEs in interaction with other drugs.(56)

Our understanding of the safety profile of CBD in children is based on data from RCTs and single-arm trials.(57) RCTs offer some limitations; they do not capture rare AEs and exclude seriously ill patients.(58). Sparse studies report on the long-term safety of CBD in the literature.

The duration of follow-up in CBD-related single arm trials is up to 2 years, and they lack control group.(59) Through this study, we synthesized evidence on the real-world safety of CBD in children to inform the current clinical guidance and increase awareness of the importance of monitoring AEs and drug interactions in children receiving CBD. Our summarized drug interaction evidence is from case reports, case series, retrospective chart reviews, and observational studies with a limited number of patients. Three single-arm trials(40, 42, 43) and two RCTs(41, 45) reported CBD-related clinical drug interactions, but their sample sizes were very small and underpowered. CBD has multiple pharmacological targets with potential therapeutic benefits and a risk of AEs. Considering its expanding use, there is a need to understand better the safety profile of CBD and its potential to interact with other drugs in children and adolescents.

3.6.1 Limitations

This study has certain limitations. We used publicly available data with limited information on prescribing trends, doses, past medical history, and temporal relationships of AEs. Data from spontaneous reports are subject to selective reporting, overreporting, and underreporting biases. We conducted a disproportionality analysis to generate signals but failed to individually determine the causality of signals generated and suspected AEs with CBD. We were also unable to assess the contribution of the other medications to the experience of the suspected AEs. Second, we could not establish a relationship between different CBD doses, duration of use, and suspected AEs. This study lacks the calculation of the real-time incidence rate of suspected AEs. In the systematic review, case reports and small case series were the primary sources of CBD-related drug interaction evidence, highlighting lack of methodological rigor. Furthermore, based on quality assessment, most of the included studies had an unclear risk

of bias. Most studies did not explore bidirectional drug interactions between CBD and its interacting drugs. They did not report on the effect of drug interaction on the effectiveness of interacting drugs (except clobazam).

3.6.2 Future research directions

Considering the expanding use of CBD, there is a need to generate long-term safety data on CBD use in children. Causality assessment of CBD with the suspected AEs and signals generated should be performed in the real world. CBD has a strong potential to interact with other drugs, and there is a need for clinical guidelines focused on AE monitoring and therapeutic drug monitoring of CBD and co-administered drugs. CBD-drug interactions should be studied in a bidirectional way, measuring the concentration and benefits of CBD and other administered drugs. The bidirectional effect of drug interaction between CBD and clobazam on their effectiveness is well-studied. However, the mechanism of drug interaction between CBD and other drugs, such as brivaracetam, levetiracetam, and zonisamide, should be studied using well-designed pharmacokinetic studies. Additionally, there is a need to explore the dose-response relationship between CBD and interacting drugs. Real-world pharmacoepidemiologic studies on CBD and clobazam should be designed to study the long-term safety of this drug interaction.

3.7 Conclusion

Given the expanded use of CBD, there is a need to understand its complex pharmacological profile in terms of safety and interactions with other drugs in children. Strong signals for seizures, sudden unexplained death, death, hospitalization, and falls were identified with CBD. We also identified a higher prevalence of infections and pneumonia in the included reports. Clobazam, levetiracetam, and valproic acid were common suspect and concomitant drugs in spontaneous reports, and CBD is reported to interact with these drugs. Physicians need

to have open discussions with parents and patients on the potential benefits and harms of CBD and inform them about the lack of long-term safety data on CBD, as well as its potential to interact with other medications. Physicians managing children on CBD should be cautious and vigilant to monitor for AEs and adjust doses of CBD and other drugs to mitigate the risk of negative effects. There is a need for future clinical research studies on the long-term safety of CBD and pharmacokinetic studies on its drug interactions with other commonly used medications.

3.8 Acknowledgment

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3.9 Author contribution statement

MC Conceptualization, Methodology, Data curation, Visualization, Writing – original draft, Writing – review & editing, Data curation; ML Data curation, Writing – review & editing, SP, GJ, YF, and MG, Writing – review & editing; LEK Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Writing – review & editing.

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3.11 Figures

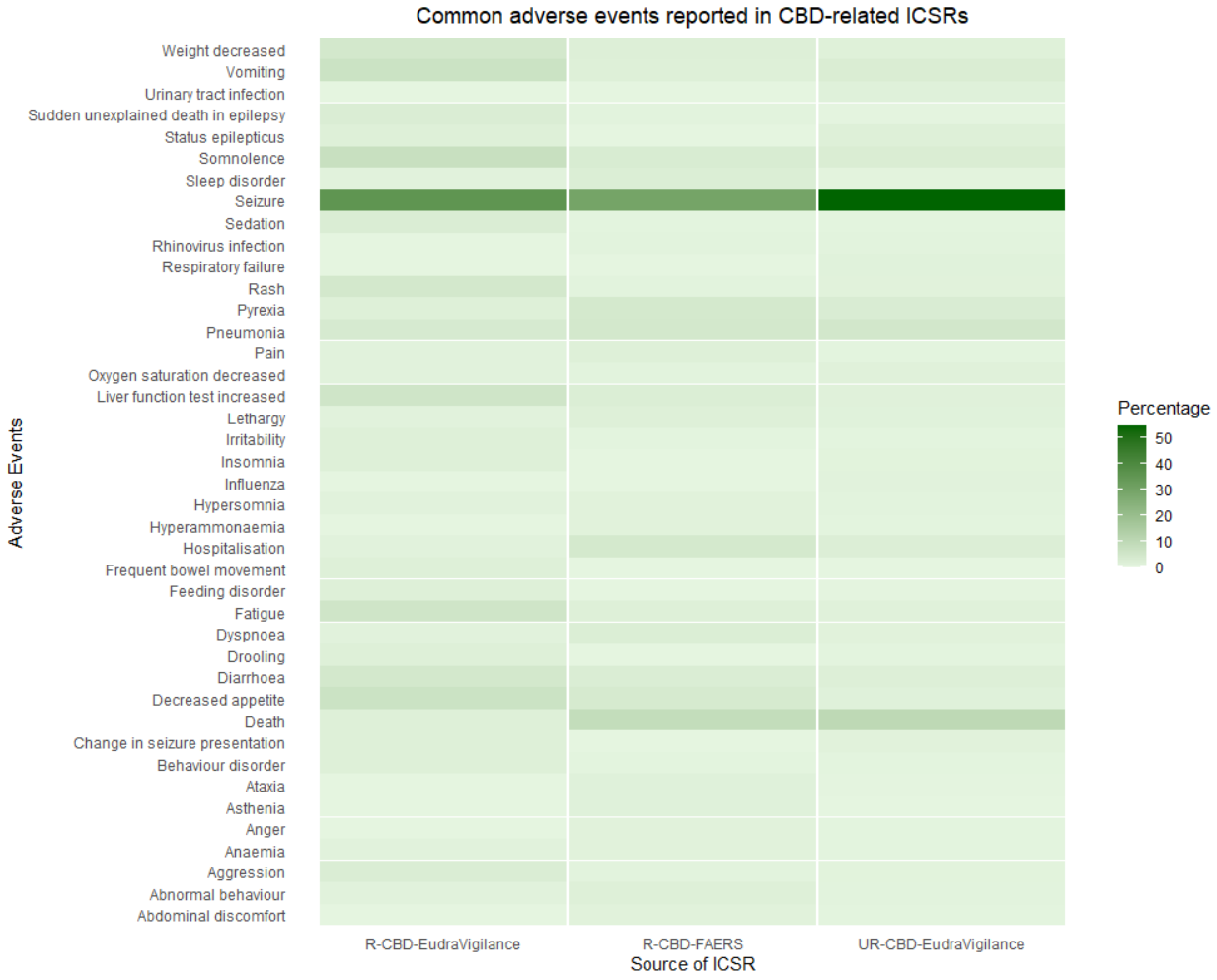


Figure 3.1. Common suspected AEs reported (>1) in the CBD-related ICSRs.

3.12 Tables

Table 3.1. Characteristics of CBD-related spontaneous reports in the FAERS.

Variables	FAERS CBD regulated (n=274), N (%)
Age Mean ± SD (yr)	9.3 ± 5.08
Age Median (Range) (yr)	9 (0.5-18)
Sex	
Male	144 (52.6)
Female	114 (41.6)
Not specified	16 (5.8)
Age group	
Infant (<2 years)	9 (2.6)
Early Childhood (2-5 years)	61 (22.3)
Middle Childhood (6-11 years)	96 (35)
Adolescence (12-18 years)	101 (36.9)
Unknown	7 (2.6)
Source of report	
Healthcare professional	165 (60)
Consumer	104 (38)
Not specified	5 (2)
Seriousness of AEs	
Serious	213 (77.7)
Non-serious	61 (22.3)
Outcomes of AEs	
Hospitalized	114 (42)
Other Outcomes	113 (41)
Died	34 (12)
Disabled	6 (2)
Life-threatening	4 (1)
Intervention required	3 (1)
Countries	
US	199 (73%)
Not Specified	34 (12%)
Italy	10 (3.6%)
Israel	6 (2.2%)
Germany	6 (2.2%)
Canada	5 (1.8%)
France	4 (1.5%)
UK	5 (1.8%)
Japan	2 (0.7%)
Netherlands	1 (0.4%)
Taiwan	1 (0.4%)
Spain	1 (0.4%)
Median (range) suspect medications	1 (1-20)
Median (range) concomitant medications	1 (1-16)
Median (range) total medications	2 (2-21)
Indication	
Epilepsy	132 (48.2)
Unknown Indication	72 (26.3)
Refractory epilepsy#	45 (16.4)
Off-label use	4 (1.5)

Tuberous Sclerosis Complex	4 (1.5)
Others*	18 (6.2)

*Pain, Panic Attack, Paroxysmal Sympathetic Hyperactivity, Prophylaxis, Rett Syndrome, Sleep Disorder, Tuberculosis, Cystic Fibrosis, Evidence Based Treatment, Immunodeficiency Common Variable, Immunosuppression, Mental Disorder, Autism Spectrum Disorder, Behaviour Disorder, Anxiety, Abnormal Faeces; # Severe Myoclonic Epilepsy of Infancy, Status Epilepticus, Infantile Spasms, Epileptic Encephalopathy, Aicardi's Syndrome, Angelman's Syndrome, Cdkl5 Deficiency Disorder

Table 3.2. Characteristics of CBD-related spontaneous reports in the EudraVigilance.

Variables	EudraVigilance	
Demographic	**Regulated CBD (n=104), N (%)**	**Unregulated CBD (n=1690), N (%)**
Healthcare Professional	89 (86)	1661 (98)
Non-healthcare Professional	15 (14)	29 (1.7)
Area		
European Economic area	84 (81)	87 (5.1)
Non-European Economic area	20 (19)	1603 (95)
Sex		
Male	59 (57)	873 (52)
Female	37 (36)	807 (48)
Not specified	8 (7.7)	10 (0.6)
Age group		
2 months – 2 years	7 (6.7)	151 (8.9)
3-11 years	62 (60)	914 (54)
12-17 years	35 (34)	624 (37)
Suspect/interacting		
Suspect	99 (95)	1664 (98.5)
Interacting	5 (4.8)	26 (1.5)
Outcome of AEs		
Unknown	136 (52.5)	2360 (60)
Recovered/Resolved	73 (28.2)	619 (16)
Not Recovered/Not Resolved	21 (8.1)	493 (13)
Fatal	7 (2.7)	273 (7)
Recovering/Resolving	22 (8.5)	149 (4)
Recovered/Resolved with Sequelae	NA	23 (1)
Median (range) suspect medications	1 (1-9)	1 (0-24)
Median (range) concomitant medications	1 (0-7)	0 (0-36)
Median (range) total medications	2.5 (1-10)	1 (0-37)
Indication		
Lennox-Gastaut syndrome	36 (34.6)	613 (44)
Epilepsy	27 (26)	743 (36.3)
Product used for unknown indication	19 (18.3)	205 (12.1)
Severe myoclonic epilepsy of infancy	11 (10.6)	44 (2.6)
Tuberous sclerosis complex	4 (3.8)	12 (0.7)
Encephalopathy	2 (1.9)	6 (0.4)
Infantile Spasm	1	11 (0.7)
Cerebral palsy	0	6 (0.4)
Status epilepticus	0	4 (0.2)
Autism spectrum disorder	0	3 (0.2)
Febrile infection	0	3 (0.2)
Spasticity	0	3 (0.2)
Rett syndrome	1	2 (0.1)
Not reported	0	17 (1)
Unclear	0	2 (0.1)
Other	2 (1.9) *	16 (0.9) #

*One each Aicardi's syndrome, CSWS syndrome

Jeavons syndrome, pain, somnolence, palliative care, anti-inflammatory therapy, Arthralgia, Psychomotor hyperactivity, Cystic fibrosis, Brain cancer, Aicardi's syndrome, Neuromyopathy, Brain malformation, Angelman's syndrome, Anxiety, Metachromatic leukodystrophy, Encephalopathy

Table 3.3. Positive signals for suspected AEs associated with CBD as a primary suspect.

Adverse event	n	PRR 95% CI	ROR 95% CI	Chi-square with Yate's correction
Seizure	328	19.77 (18.03-21.67)	28.97 (25.33-33.13)	5658.60
Sudden unexplained death in epilepsy	4	27.64 (10.07-75.91)	27.75 (10.06-76.50)	72.90
Status epilepticus	7	2.28 (1.09-4.79)	2.30 (1.10-4.83)	3.836
Fall	14	2.81 (1.67-4.74)	2.84 (1.67-4.82)	14.56
Head injury	6	4.46 (1.99-9.94)	4.48 (1.99-10.04)	12.70
Sedation	6	2.75 (1.24-6.13)	2.77 (1.24-6.19)	5.04
Behavior disorder	4	3.33 (1.25-8.89)	3.34 (1.25-8.95)	4.37
Decreased appetite	20	2.09 (1.35-3.22)	2.11 (1.35-3.2)	10.27
Weight decreased	23	2.67 (1.80-4.03)	2.73 (1.80-4.14)	22.85
Death	176	14.07 (12.27-16.13)	16.88 (14.31-19.90)	2081.15
Hospitalization	127	30.83 (26.03-36.51)	35.18 (29.03-42.64)	3399.03
Pneumonia	32	2.76 (1.96-3.89)	2.82 (1.98-4.01)	34.29
Aspiration	7	6.34 (3.01-13.33)	6.37 (3.01-13.48)	25.97
Viral infection	9	2.13 (1.11-4.09)	2.14 (1.11-4.13)	4.32
Rhinovirus infection	5	3.51 (1.46-8.45)	3.526 (1.46-8.52)	6.60

Table 3.4 Summary of the CBD-related DDIs findings from a systematic review.

CBD type	Studies	Interacting drugs	Type	Mechanism	Outcome	Recommendations	References
Purified CBD	3 studies case report (1), and retrospective chart review (2)	mTOR inhibitors (EVE and SRL)	PK	CBD Inhibits CYP3A4	Increase in plasma levels of EVE and SRL, adverse event involuntary movements	Monitor blood levels, dose reduction for temisirolimus, EVE, and SRL, may be required	(41, 50, 52)
Purified CBD	4 studies case report 1, retrospective chart review (1), observational (1), and RCT 1	VPA	PK and PD	CBD inhibits UGT	Increase in plasma levels of VPA, resulting in increase in LFTs, decrease in PLTs, one study reported decrease in plasma VPA levels	Monitor closely, especially for LFTs, platelet count, and VPA plasma levels	(39, 51, 53, 55)
Purified CBD	1 study, case report (1)	Lithium	PK	CBD reduces renal clearance of Lithium	Increase in plasma levels of lithium	Monitor lithium plasma levels, lithium dose may need to be reduced	(40)
Purified CBD	8 studies, case series (2), observational (2), NRT (3), and RCT (1)	CLB	Bidirectional PK	CBD inhibits CYP3A4 and CYP2C19	Increase in plasma levels of n-CLB (active metabolite of CLB), CLB also increases CBD levels	Monitor closely, may require CLB and/or CBD dose reduction	(44, 46-49, 53, 56)
Purified CBD	1 study, case series (1)	Levothyroxine	PK	Levothyroxine inhibits CYP3A4	Levothyroxine increases plasma level of CBD	Monitor closely	(43)
Purified CBD	1 study, case series (1)	Fluoxetine	PK	CBD inhibits CYP2D6	Increase in plasma level of fluoxetine (patient had null CYP2D6 variant)	Monitor closely	(42)
Purified CBD	1 study, RCT (1)	STP	PK	CBD inhibits CYP2C19	Increase in plasma levels of STP	Monitor closely; may require dose reduction of STP	(55)

Purified CBD	1 study, NRT (1)	Rufinamide	PK	Unknown	Increase in plasma levels of rufinamide	Monitor closely	(48)
Purified CBD	2 studies, observational (1) NRT (1)	TPM	PK	CBD inhibits CYP2C9 and CYP2C19	Increase in plasma levels of TPM	Monitor closely	(48, 53)
Purified CBD	2 studies, observational (1), NRT (1)	Eslicarbazepine	PK	Unknown	Increase in plasma levels of eslicarbazepine	Monitor closely	(48)
CBD-enriched CHE	2 studies, observational study (1), BRV 1 study, LEV case series (1)	LEV and BRV	PK	LEV Unknown BRV CBD inhibits CYP2C19	LEV Carboxylic acid metabolite decreases elimination of CBD, BRV Increase in plasma levels of BRV, 2/5 patients experienced diarrhea and somnolence	Monitor closely	(45, 54)
CBD-enriched CHE	2 studies, observational study (1), NRT (1)	ZNS	PK	Unknown	ZNS increases volume of distribution and decreases elimination of CBD	Monitor closely, may require CBD dose reduction	(48, 54)
CBD-enriched CHE	1 study, case report	Methadone	PK	CBD inhibits CYP3A4 and CYP2C19	Increase in plasma levels of Methadone, resulting in sedation	Monitor clinical response	(38)

Abbreviations BRV Brivaracetam, CBD Cannabidiol, CLB Clobazam, CYP Cytochrome, EVE Everolimus, LEV Levetiracetam, NRT Non-randomized trial, PK Pharmacokinetic, PD Pharmacodynamic, RCT Randomized Controlled Trial, SRL Sirolimus, STP Stiripentol, TPM topiramate, VPA Valproic acid, ZNS Zonisamide

3.13 Appendix A

3.13.1 Methods for systematic review

3.13.1.1 CBD-related drug interactions systematic review

The systematic review protocol was registered with PROSPERO (CRD42020187433). The systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA),(1) PRISMA-S guidelines,(2) and Cochrane collaboration guidelines.(3) This is a secondary analysis from the living systematic review published elsewhere (under peer review) that included literature on cannabinoids used for medical purposes in children. We included studies reporting CBD-related clinical drug interactions where CBD was used as an intervention or treatment of self-reported medical intent and included children aged 18 years or younger. The primary outcome of this subgroup systematic review was to collect evidence on CBD-related drug interactions (pharmacokinetic and pharmacodynamic) in children. The secondary outcome was to quantify the effect of drug interaction on safety and effectiveness outcomes.

3.13.1.2 Literature searches

An experienced health sciences librarian (ML) searched MEDLINE (Ovid), Embase (Ovid), PsycInfo (Ovid), and the Cochrane Library (Wiley). The complete database search strategies for the LSR are available in the **supplementary material** and elsewhere.(4) Citations retrieved from the literature were imported to Endnote® for deduplication and then uploaded to Covidence® for screening.

3.13.1.3 Study selection, data extraction, and quality assessment

Two reviewers independently performed the first pass (title and abstract), second pass screening (full-text screening), data extraction, and quality assessment. Conflicts between pairs

of reviewers were resolved by contacting a third reviewer (LEK). Data extraction was done for characteristics of included studies, study participants, cannabinoids, drug interactions (type, interacting drugs, concomitant drugs, and outcome), effectiveness and safety findings. Quality assessment was performed using Cochrane risk of bias1 (ROB1) tool,(5) Joanna Briggs Institute (JBI) checklist for quasi-experimental design,(6) JBI critical appraisal checklist for case series(7) and JBI critical appraisal checklist for case reports.(8) Data extraction and quality assessment was completed in Microsoft excel 2019.

3.13.1.4 Data synthesis

Narrative synthesis of the extracted data was performed using Microsoft Excel 2019. Studies did not report any quantitative data, and synthesis without meta-analysis (SWiM) guidelines were followed to synthesize evidence.(9)

3.13.2 Result

19 unique studies reporting CBD-related drug interactions in children were included four case reports,(10-13) five case series,(14-18) three single-arm trials,(19-21) three treatment chart reviews,(22-24) two observational studies,(25, 26) and two randomized controlled trials(27, 28) were included. **eFigure 1.** Illustrates the complete process of study selection using the PRISMA flow diagram. Twelve studies were from the US,(10, 12, 16, 19-26, 28) two from Germany,(13, 17) and one each from Argentina,(15) Australia,(14) France,(18) Italy,(11) the Netherlands,(27) Spain,(27) Sweden,(27) and the UK. (28) Purified CBD and CBD-enriched CHEs Cannabis Herbal Extracts (CHEs) were the common types of CBD used in children in the included studies. In 73.6% (n=13/19) of the studies, CBD was used for drug-resistant epilepsy (DRE)(11, 15-21, 23, 25-28) followed by tuberous sclerosis complex (TSC)(13, 22, 24) in 15.7% (n=3/19) of the

studies, ASD(12, 14) in 10.5% (n=2/19) of the study studies, and cancer in 5.2% (n=1/19) of the studies.(10)

3.13.2.1 Quality assessment

One case report had unclear internal quality,(11) and other(10) had inadequate quality (lack of reporting on patient history and clinical conditions) on the JBI critical appraisal checklist for case reports. In case series, treatment chart reviews, and observational studies, two had inadequate quality(14, 22) and two had unclear(18, 24) quality on the JBI critical appraisal checklist for case series. RCTs had unclear risk of bias(27, 28) due to lack of information on random sequence generation, allocation concealment, and blinding in one RCT(27) and blinding in another RCT(28) using the Cochrane ROB1 tool. **eFigures 3.2, 3.3, 3.4, and 3.5** provide a complete summary of the quality assessment of the included studies.

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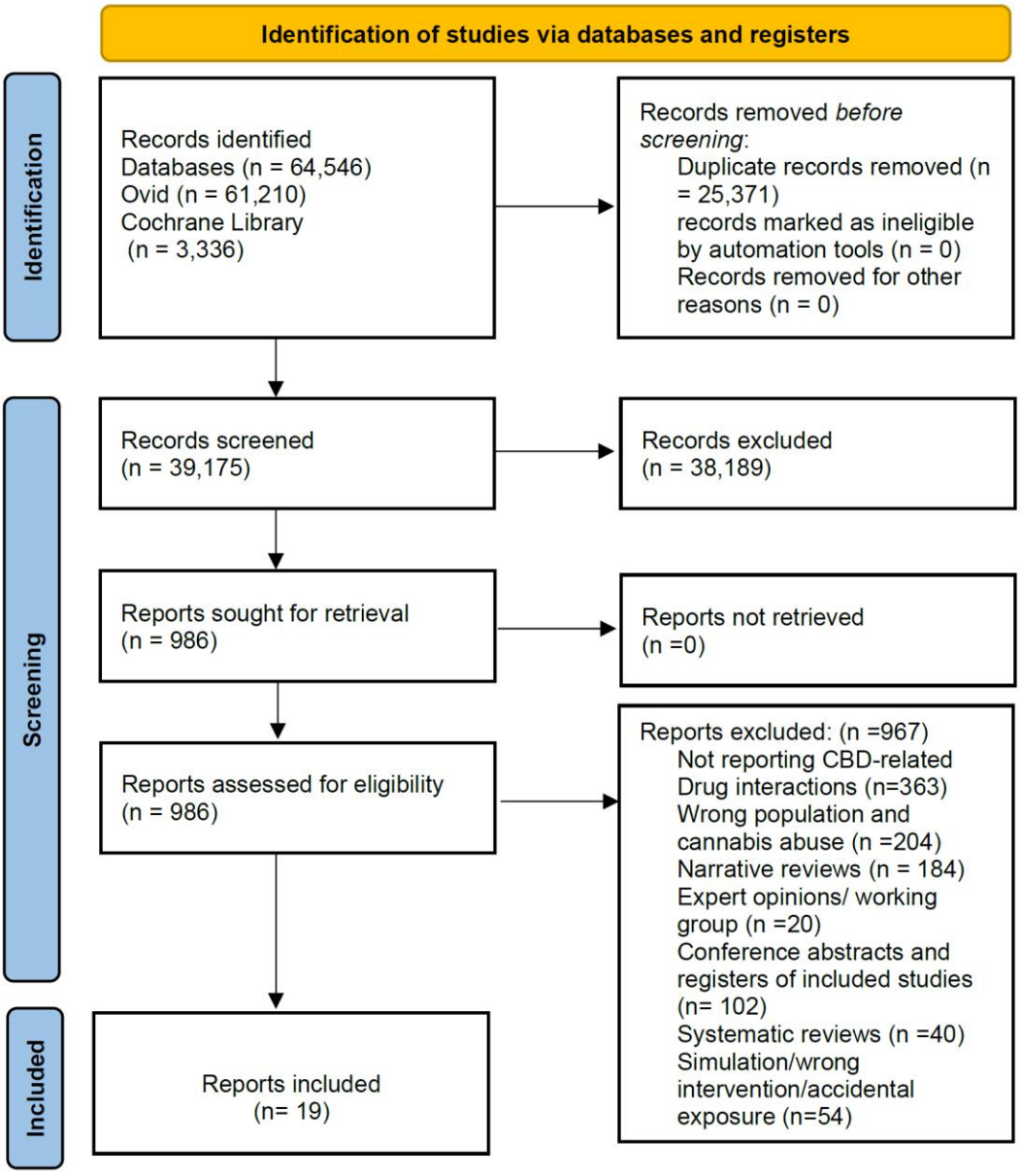
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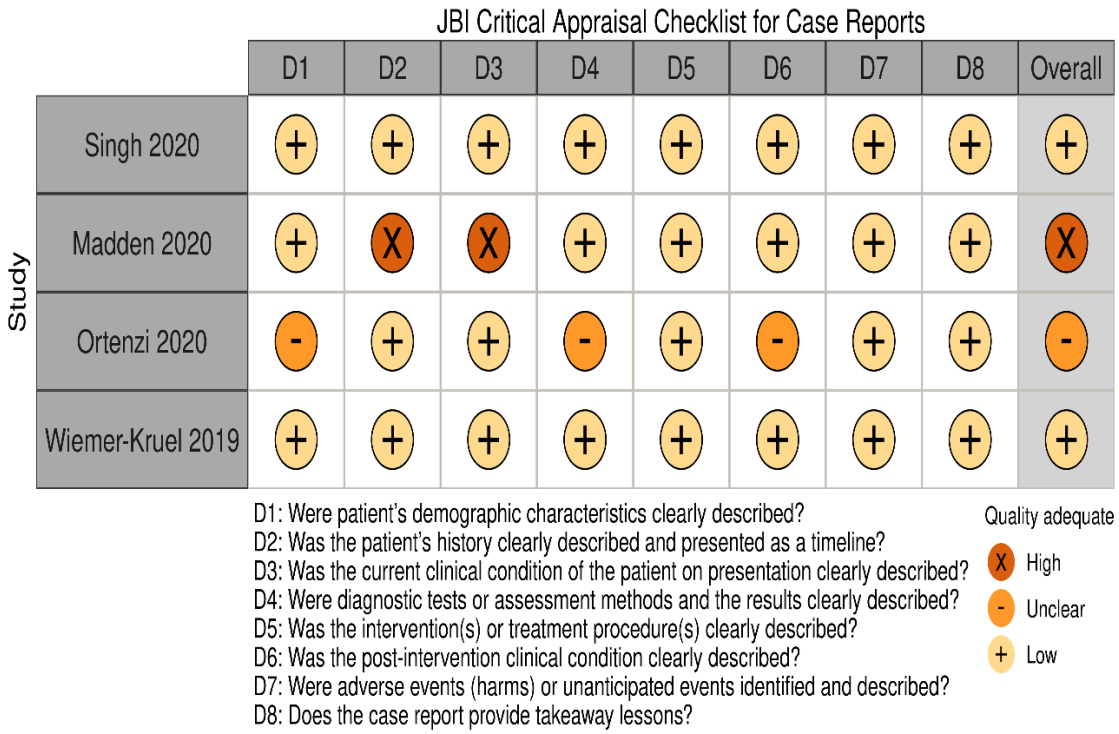
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3.14 Supplementary material

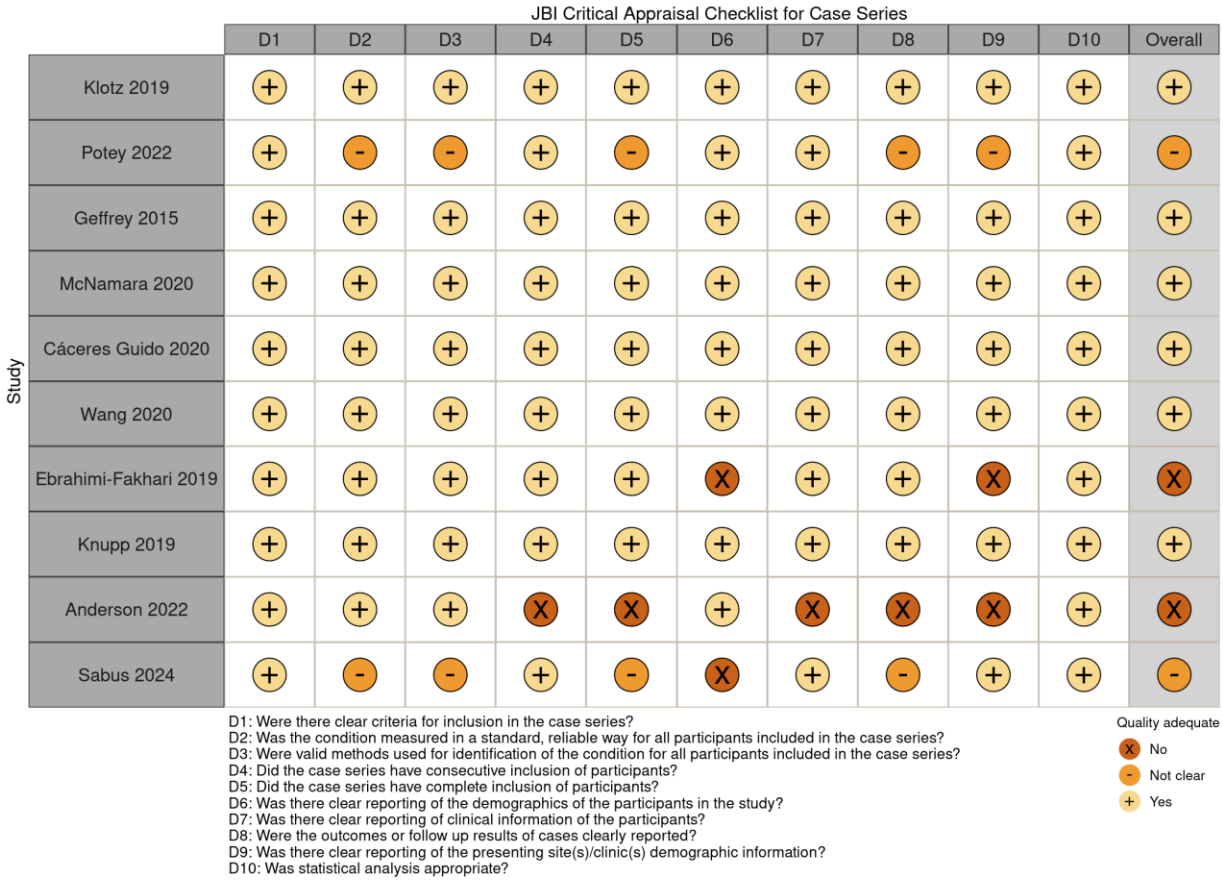
3.14.1 eFigures



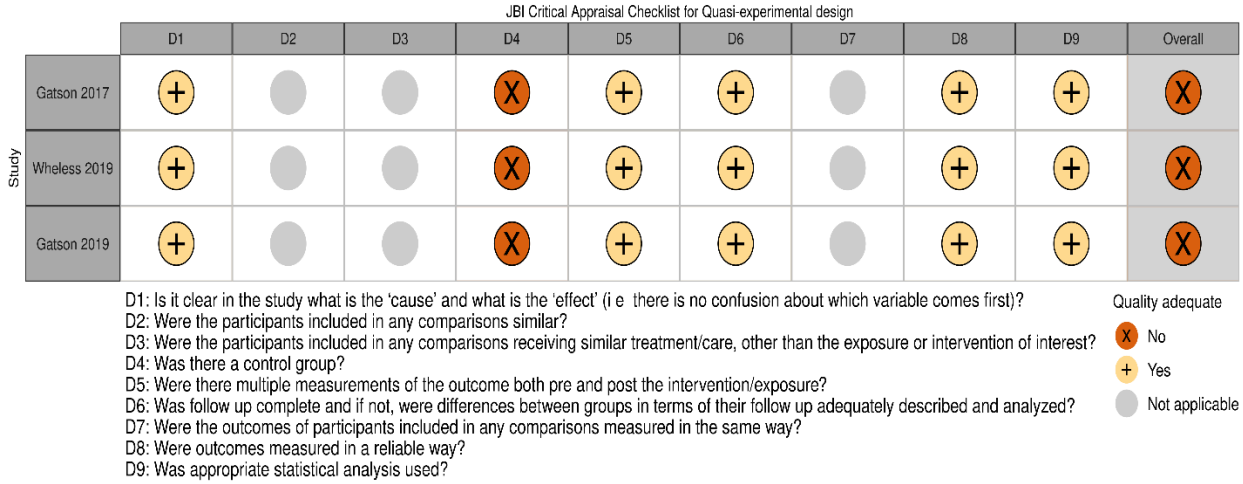
eFigure 3.1. The PRISMA flow diagram for the included studies.



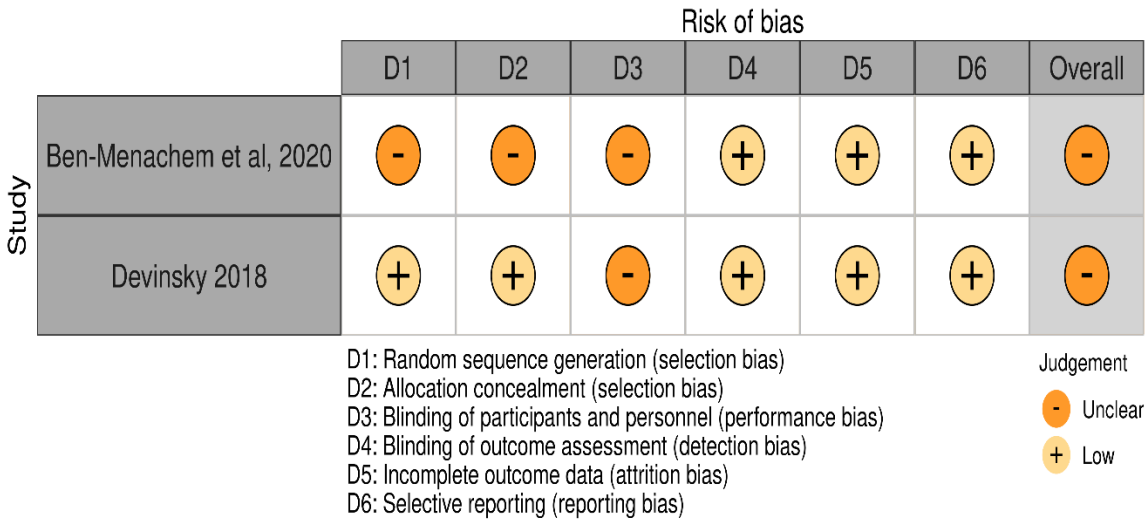
eFigure 3.2. Summary of the quality assessment of the case reports.



eFigure 3.3. Summary of the quality assessment of the observational studies (case series, chart reviews, and cohort studies).



eFigure 3.4. Summary of the quality assessment of the single-arm studies.



eFigure 3.5. Summary of the quality assessment of the RCTs.

3.14.2 eTables

eTable 3.1. Calculation of PRR, and ROR.

	AE of interest	All other AEs	Total	Formula
Medication of interest	A	B	A+B	$PRR = \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$
All other medications	C	D	C+D	$ROR = \frac{A/B}{C/D}$

eTable 3.2. Common suspect and concomitant medications reported with CBD in the spontaneous reports.

Suspect medications with CBD (>1%)	**FAERS n (%) (n=274)**	**EudraVigilance Regulated CBD n (%) (n=104)**	**EudraVigilance Unregulated CBD n (%) (n=1690)**
Clobazam	30 (11)	13 (13)	66 (4)
Valproic Acid	27 (10)	15 (14)	50 (3)
Levetiracetam	24 (9)	2 (2)	32 (2)
Vigabatrin	15 (5)	0	14 (1)
Lamotrigine	12 (4)	0	13 (1)
Topiramate	10 (4)	2 (2)	30 (2)
Fenfluramine	10 (4)	2 (2)	3 (0.2)
Perampanel	8 (3)	0	11 (1)
Stiripentol	8 (3)	0	6 (0.3)
Phenobarbital	7 (3)	2 (2)	30 (2)
Carbamazepine	6 (2)	0	11 (1)
Lacosamide	6 (2)	0	14 (1)
Phenytoin	6 (2)	0	3 (0.2)
Rufinamide	6 (2)	0	11 (1)
Potassium Bromide	5 (2)	1 (1)	3 (0.2)
Zonisamide	5 (2)	0	4 (0.24)
Clonazepam	0	0	11 (1)
Concomitant medications (>2%)			
Clobazam	47 (17)	30 (29)	284 (16.8)
Levetiracetam	32 (12)	10 (10)	201 (11.9)
Valproic acid	14 (5)	12 (12)	123 (7.3)
Lamotrigine	13 (5)	11 (11)	76 (4.5)
Diazepam	12 (4)	2 (2)	117 (6.9)
Albuterol	11 (4)	0	0
Clonazepam	11 (4)	3 (3)	108 (6.4)
Vitamin D	11 (4)	0	10 (0.6)
Baclofen	10 (4)	0	46 (2.7)
Lorazepam	9 (3)	0	29 (1.7)
Levocarnitine	8 (3)	2 (2)	40 (2.4)
Topiramate	7 (3)	6 (6)	96 (5.7)
Polyethylene Glycols	7 (3)	0	0
Lacosamide	7 (3)	4 (4)	78 (4.6)
Zonisamide	7 (3)	3 (3)	52 (3.1)
Oxcarbazepine	6 (2)	0	33 (2.1)
Rufinamide	5 (2)	6 (6)	67 (4)
Felbamate	5 (2)	3 (3)	16 (0.9)
Budesonide	5 (2)	0	37 (2.2)
Fluticasone	5 (2)	0	74 (4.4)
Vigabatrin	5 (2)	0	62 (3.7)
Lansoprazole	5 (2)	0	38 (2.2)
Melatonin	5 (2)	4 (4)	59 (3.5)

Stiripentol	0	5 (5)	6 (0.4)
Midazolam	0	3 (3)	29 (1.7)
Cannabis flowers	0	2 (2)	1 (0.1)
Everolimus	0	2 (2)	3 (0.2)
Perampanel	0	2 (2)	36 (2.1)
Phenytoin	0	2 (2)	10 (0.6)
Pregabalin	0	2 (2)	3 (0.2)
Primidone	0	2 (2)	1 (0.1)

eTable 3.3. Comprehensive list of suspected adverse events reported in the identified ICSRs.

Suspected Adverse Events (AEs)	EudraVigilance		FAERS
	UR CBD-Eudra (n=1690)	R CBD-Eudra (n=104)	R CBD-FAERS (n=274)
CNS and psychiatry related Suspected AEs			
Seizure	923 (54.6)	37 (35.6)	82 (29.9)
Somnolence	50 (3)	8 (7.7)	9 (3.3)
Sudden unexplained death in epilepsy	4 (0.2)	3 (2.9)	2 (0.7)
Status epilepticus	30 (1.8)	2 (1.9)	3 (1.1)
Change in seizure presentation	18 (1.1)	2 (1.9)	0
Insomnia	15 (0.9)	2 (1.9)	0
Amnesia	1 (0.1)	2 (1.9)	0
Sleep disorder	10 (0.6)	1 (1)	5 (1.8)
Pain	6 (0.4)	1 (1)	5 (1.8)
Hypersomnia	11 (0.7)	1 (1)	3 (1.1)
Tremor	6 (0.4)	1 (1)	1 (0.4)
Cognitive disorder	1 (0.1)	1 (1)	1 (0.4)
Disturbance in attention	3 (0.2)	1 (1)	1 (0.4)
Feeling abnormal	2 (0.1)	1 (1)	0
Feeling drunk	1 (0.1)	1 (1)	0
Abnormal behaviour	11 (0.7)	1 (1)	5 (1.8)
Lethargy	0	0	5 (1.8)
Ataxia	3 (0.2)	0	4 (1.5)
Anger	6 (0.4)	0	3 (1.1)
Aggression	15 (0.9)	3 (2.9)	2 (0.7)
Irritability	8 (0.5)	2 (1.9)	2 (0.7)
Loss of consciousness	4 (0.2)	0	2 (0.7)
Poor quality sleep	3 (0.2)	0	2 (0.7)
Staring	2 (0.1)	0	2 (0.7)
Euphoric Mood	0	1 (1)	2 (0.7)
Fall	31 (1.8)	0	1 (0.4)
Agitation	12 (0.7)	0	1 (0.4)
Sedation	8 (0.5)	3 (2.9)	1 (0.4)
Anxiety	6 (0.4)	0	1 (0.4)
Behaviour disorder	6 (0.4)	2 (1.9)	1 (0.4)
Coma	6 (0.4)	0	1 (0.4)
Depression	3 (0.2)	0	1 (0.4)
Headache	3 (0.2)	0	1 (0.4)
Mood swings	4 (0.2)	0	1 (0.4)

Dysarthria	2 (0.1)	0	1 (0.4)
Dyskinesia	2 (0.1)	0	1 (0.4)
Shock	3 (0.2)	0	1 (0.4)
Autism spectrum disorder	1 (0.1)	0	1 (0.4)
Decreased activity	1 (0.1)	0	1 (0.4)
Decreased interest	1 (0.1)	0	1 (0.4)
Dizziness	1 (0.1)	0	1 (0.4)
Head banging	1 (0.1)	0	1 (0.4)
Daydreaming	0	0	1 (0.4)
Electroencephalogram Abnormal	0	0	1 (0.4)
Mania	0	0	1 (0.4)
Movement Disorder	0	0	1 (0.4)
Neuroprosthesis Implantation	0	0	1 (0.4)
Social Avoidant Behaviour	0	0	1 (0.4)
Asthenia	13 (0.8)	0	0
Head injury	10 (0.6)	0	0
Balance disorder	9 (0.5)	0	0
Brain operation	8 (0.5)	0	0
Gait disturbance	8 (0.5)	0	0
Crying	7 (0.4)	0	0
Psychomotor hyperactivity	7 (0.4)	0	0
Suicidal ideation	6 (0.4)	0	0
Unresponsive to stimuli	6 (0.4)	0	0
Confusional state	5 (0.3)	0	0
Dystonia	5 (0.3)	0	0
Hypotonia	5 (0.3)	0	0
Hallucination	4 (0.2)	0	0
Restlessness	4 (0.2)	1 (1)	0
Brain oedema	3 (0.2)	0	0
Contusion	3 (0.2)	0	0
Facial paralysis	3 (0.2)	0	0
Mental status changes	3 (0.2)	0	0
Muscle twitching	3 (0.2)	0	0
Screaming	3 (0.2)	0	0
Sleep apnoea syndrome	3 (0.2)	0	0
Akathisia	2 (0.1)	0	0
Attention deficit hyperactivity disorder	2 (0.1)	0	0
Coordination abnormal	2 (0.1)	0	0
Craniofacial fracture	2 (0.1)	0	0
Depressed level of consciousness	2 (0.1)	0	0
Disorientation	2 (0.1)	0	0
Drug withdrawal symptoms	2 (0.1)	1 (1)	0

Encephalopathy	2 (0.1)	0	0
Malignant cranial nerve neoplasm	2 (0.1)	0	0
Metastases to spine	2 (0.1)	0	0
Nerve compression	2 (0.1)	0	0
Nervous system disorder	2 (0.1)	0	0
Neuroblastoma recurrent	2 (0.1)	0	0
Panic attack	2 (0.1)	0	0
Post procedural haemorrhage	2 (0.1)	0	0
Sedation complication	2 (0.1)	0	0
Speech disorder	2 (0.1)	0	0
Vagal nerve stimulator implantation	2 (0.1)	0	0
Vertigo	2 (0.1)	0	0
Acute disseminated encephalomyelitis	1 (0.1)	0	0
Affect lability	1 (0.1)	0	0
Apathy	1 (0.1)	0	0
Aphasia	1 (0.1)	0	0
Autoimmune encephalopathy	1 (0.1)	0	0
Autonomic nervous system imbalance	1 (0.1)	0	0
Brain death	1 (0.1)	0	0
Brain injury	1 (0.1)	0	0
Cerebral calcification	1 (0.1)	0	0
Cerebral capillary telangiectasia	1 (0.1)	0	0
Cerebral haemorrhage	1 (0.1)	0	0
Cerebral palsy	1 (0.1)	0	0
Communication disorder	1 (0.1)	0	0
Completed suicide	1 (0.1)	0	0
Cortical visual impairment	1 (0.1)	0	0
Defiant behaviour	1 (0.1)	0	0
Diabetic coma	1 (0.1)	0	0
Drug abuse	1 (0.1)	0	0
Dysphemia	1 (0.1)	0	0
Emotional distress	1 (0.1)	0	0
Encephalitis	1 (0.1)	0	0
Encephalitis autoimmune	1 (0.1)	0	0
Encephalomalacia	1 (0.1)	0	0
Epileptic encephalopathy	1 (0.1)	0	0
Fear	1 (0.1)	0	0
Food aversion	1 (0.1)	0	0
Head titubation	1 (0.1)	0	0
Hemiparesis	1 (0.1)	0	0
Hypervigilance	1 (0.1)	1 (1)	0
Impulsive behaviour	1 (0.1)	0	0

Inappropriate antidiuretic hormone secretion	1 (0.1)	0	0
Intermittent explosive disorder	1 (0.1)	0	0
Mental impairment	1 (0.1)	0	0
Migraine	1 (0.1)	0	0
Moaning	1 (0.1)	0	0
Nervousness	1 (0.1)	0	0
Neurodegenerative disorder	1 (0.1)	0	0
Neurogenic bladder	1 (0.1)	0	0
Neuronal ceroid lipofuscinosis	1 (0.1)	0	0
Paraesthesia	1 (0.1)	0	0
Paranoia	1 (0.1)	0	0
Postictal state	1 (0.1)	0	0
Psychotic disorder	1 (0.1)	1 (1)	0
Pulseless electrical activity	1 (0.1)	0	0
Rasmussen encephalitis	1 (0.1)	0	0
Restless legs syndrome	1 (0.1)	0	0
Spinal operation	1 (0.1)	0	0
Tardive dyskinesia	1 (0.1)	0	0
Temperature intolerance	1 (0.1)	0	0
Trichotillomania	1 (0.1)	0	0
Photophobia	0	1 (1)	0
Poverty of speech	0	1 (1)	0
Product-related AEs/ medication errors			
Off label use	59 (3.5)	9 (8.7)	33 (12)
Drug ineffective	83 (4.9)	5 (4.8)	30 (10.9)
Drug interaction	31 (1.8)	5 (4.8)	12 (4.4)
Intentional dose omission	2 (0.1)	0	7 (2.6)
Therapeutic response unexpected	1 (0.1)	5 (4.8)	5 (1.8)
Therapy Cessation	0	0	4 (1.5)
Product supply issue	71 (4.2)	0	4 (1.5)
Drug ineffective for unapproved indication	6 (0.4)	0	4 (1.5)
Prescribed overdose	45 (2.7)	0	3 (1.1)
Product quality issue	3 (0.2)	1 (1)	2 (0.7)
Incorrect dose administered	10 (0.6)	0	2 (0.7)
Drug resistance	1 (0.1)	0	2 (0.7)
Treatment noncompliance	1 (0.1)	0	2 (0.7)
Overdose	17 (1)	3 (2.9)	1 (0.4)
Product physical issue	6 (0.4)	1 (1)	1 (0.4)
Product colour issue	2 (0.1)	1 (1)	1 (0.4)
Intentional underdose	0	0	1 (0.4)
Inappropriate affect	1 (0.1)	0	1 (0.4)
Prescription drug used without a prescription	1 (0.1)	0	1 (0.4)

Product formulation issue	1 (0.1)	0	1 (0.4)
Product preparation issue	1 (0.1)	0	1 (0.4)
Drug effective for unapproved indication	3 (0.2)	0	1 (0.4)
Drug intolerance	2 (0.1)	0	1 (0.4)
Product temperature excursion issue	1 (0.1)	1 (1)	0
Product administration interrupted	5 (0.3)	1 (1)	0
Economic problem	0	1 (1)	0
Intentional product misuse	3 (0.2)	0	0
Intentional removal of drug delivery system by patient	1 (0.1)	0	0
Medical device battery replacement	1 (0.1)	0	0
Product closure issue	1 (0.1)	0	0
Product complaint	1 (0.1)	0	0
Product design issue	1 (0.1)	0	0
Product leakage	1 (0.1)	0	0
Product odour abnormal	1 (0.1)	0	0
Product prescribing error	1 (0.1)	0	0
Product residue present	1 (0.1)	0	0
Product substitution issue	1 (0.1)	0	0
Product use issue	38 (2.2)	0	0
Incorrect route of product administration	35 (2.1)	0	0
Product administered to patient of inappropriate age	17 (1)	0	0
Insurance issue	13 (0.8)	0	0
Circumstance or information capable of leading to medication error	6 (0.4)	0	0
Product container issue	6 (0.4)	0	0
Product prescribing issue	5 (0.3)	0	0
Toxicity to various agents	5 (0.3)	0	0
Inappropriate schedule of product administration	4 (0.2)	0	0
Therapeutic product effect decreased	4 (0.2)	0	0
Device occlusion	3 (0.2)	0	0
Complication associated with device	3 (0.2)	0	0
Incorrect dosage administered	3 (0.2)	0	0
Medical device change	3 (0.2)	0	0
Wrong dose	1 (0.1)	0	0
Product use complaint	3 (0.2)	0	0
Product dispensing issue	2 (0.1)	0	0
Product expiration date issue	2 (0.1)	0	0
Product taste abnormal	2 (0.1)	0	0
Device malfunction	3 (0.2)	0	0
Exposure to toxic agent	1 (0.1)	0	0
Overdose	1 (0.1)	0	0

Syringe issue	1 (0.1)	0	0
GI-related Suspected AEs			
Vomiting	50 (3)	7 (6.7)	5 (1.8)
Decreased appetite	25 (1.5)	7 (6.7)	11 (4)
Diarrhoea	38 (2.2)	5 (4.8)	8 (2.9)
Drooling	7 (0.4)	2 (1.9)	0
Abdominal pain upper	4 (0.2)	2 (1.9)	0
Feeding disorder	3 (0.2)	2 (1.9)	0
Frequent bowel movements	0	2 (1.9)	0
Gastrostomy tube site complication	1 (0.1)	1 (1)	0
Constipation	12 (0.7)	1 (1)	1 (0.4)
Nausea	10 (0.6)	1 (1)	1 (0.4)
Abdominal pain	8 (0.5)	1 (1)	0
Gastrostomy	2 (0.1)	1 (1)	0
Appetite disorder	0	1 (1)	0
Gingivitis	0	1 (1)	0
Insulin resistant diabetes	1 (0.1)	0	1 (0.4)
Dehydration	15 (0.9)	0	2 (0.7)
Pancreatitis	9 (0.5)	0	2 (0.7)
Abdominal discomfort	8 (0.5)	0	3 (1.1)
Gastrointestinal disorder	5 (0.3)	0	2 (0.7)
Intestinal obstruction	5 (0.3)	0	1 (0.4)
Feeding intolerance	3 (0.2)	0	1 (0.4)
Retching	2 (0.1)	0	1 (0.4)
Pancreatic failure	1 (0.1)	0	1 (0.4)
Abdominal Compartment Syndrome	0	0	1 (0.4)
Tonsillectomy	0	0	1 (0.4)
Tooth Development Disorder	0	0	1 (0.4)
Gastrectomy	1 (0.1)	0	0
Gastric haemorrhage	1 (0.1)	0	0
Gastric infection	1 (0.1)	0	0
Gastric ulcer perforation	1 (0.1)	0	0
Gastrointestinal haemorrhage	1 (0.1)	0	0
Gastrointestinal obstruction	1 (0.1)	0	0
Gastrointestinal stoma complication	1 (0.1)	0	0
Increased appetite	1 (0.1)	0	0
Infantile spitting up	1 (0.1)	0	0
Intestinal perforation	1 (0.1)	0	0
Jaw fracture	1 (0.1)	0	0
Large intestinal obstruction	1 (0.1)	0	0
Lip dry	1 (0.1)	0	0
Lip injury	1 (0.1)	0	0

Mastication disorder	1 (0.1)	0	0
Mastoiditis	1 (0.1)	0	0
Mouth haemorrhage	1 (0.1)	0	0
Mouth injury	1 (0.1)	0	0
Poor feeding infant	1 (0.1)	0	0
Procedural intestinal perforation	1 (0.1)	0	0
Hypophagia	7 (0.4)	0	0
Dysphagia	6 (0.4)	0	1 (0.4)
Discomfort	4 (0.2)	0	0
Ileus	3 (0.2)	0	0
Flatulence	3 (0.2)	0	0
Food refusal	3 (0.2)	0	0
Abdominal distension	2 (0.1)	0	0
Impaired gastric emptying	2 (0.1)	0	0
Dyspepsia	2 (0.1)	0	0
Endotracheal intubation	2 (0.1)	0	0
Femur fracture	2 (0.1)	0	0
Functional gastrointestinal disorder	2 (0.1)	0	0
Gastroesophageal reflux disease	2 (0.1)	0	0
Haematochezia	2 (0.1)	0	0
Joint swelling	2 (0.1)	0	0
Limb discomfort	2 (0.1)	0	0
Lip swelling	2 (0.1)	0	0
Abdominal operation	1 (0.1)	0	0
Abnormal faeces	1 (0.1)	0	0
Anal incontinence	1 (0.1)	0	0
Aphthous ulcer	1 (0.1)	0	0
Appendicitis	1 (0.1)	0	0
Diarrhoea haemorrhagic	1 (0.1)	0	0
Herpangina	1 (0.1)	0	0
Pancreatic neoplasm	1 (0.1)	0	0
Pancreatitis acute	1 (0.1)	0	0
Oral discomfort	1 (0.1)	0	0
Oral surgery	1 (0.1)	0	0
Oropharyngeal cobble stone mucosa	1 (0.1)	0	0
Oropharyngeal pain	1 (0.1)	0	0
Reflux gastritis	1 (0.1)	0	0
Small intestinal obstruction	1 (0.1)	0	0
Steatorrhea	1 (0.1)	0	0
General AEs			
Fatigue	23 (1.4)	6 (5.8)	5 (1.8)
Weight decreased	27 (1.6)	5 (4.8)	6 (2.2)

Malaise	3 (0.2)	3 (2.9)	0
Death	173 (10.2)	2 (1.9)	24 (8.8)
Pyrexia	53 (3.1)	2 (1.9)	12 (4.4)
Gait inability	4 (0.2)	2 (1.9)	4 (1.5)
Lethargy	20 (1.2)	1 (1)	0
Decreased activity	0	1 (1)	0
Weight increased	16 (0.9)	1 (1)	2 (0.7)
Hospitalisation	41 (2.4)	1 (1)	12 (4.4)
General physical health deterioration	3 (0.2)	1 (1)	1 (0.4)
Disease progression	1 (0.1)	1 (1)	1 (0.4)
Pallor	0	1 (1)	0
Secretion Discharge	0	1 (1)	1 (0.4)
Asthenia	0	0	4 (1.5)
Energy Increased	0	0	1 (0.4)
Emergency care	7 (0.4)	0	1 (0.4)
Loss of personal independence in daily activities	1 (0.1)	0	0
Hyperhidrosis	3 (0.2)	1 (1)	0
Mobility decreased	1 (0.1)	0	0
Post procedural complication	1 (0.1)	0	0
Quality of life decreased	1 (0.1)	0	0
Prolapse	1 (0.1)	0	0
Starvation	1 (0.1)	0	0
Intensive Care	0	0	1 (0.4)
Road traffic accident	1 (0.1)	0	0
Foetal growth restriction	1 (0.1)	0	0
Disability	1 (0.1)	0	0
Illness	11 (0.7)	0	0
Hip surgery	7 (0.4)	0	0
Surgery	6 (0.4)	0	0
Injury	4 (0.2)	0	0
Joint dislocation	3 (0.2)	0	0
Malnutrition	3 (0.2)	0	0
Peripheral swelling	3 (0.2)	0	0
Weight abnormal	3 (0.2)	0	0
Withdrawal syndrome	3 (0.2)	0	0
Abnormal loss of weight	2 (0.1)	0	0
Chills	2 (0.1)	0	0
Cyst	2 (0.1)	0	0
Face injury	2 (0.1)	0	0
Failure to thrive	2 (0.1)	0	0
Hypothermia	2 (0.1)	0	0
Poisoning	2 (0.1)	0	0

Spinal fusion surgery	2 (0.1)	0	0
Upper limb fracture	2 (0.1)	0	0
Weight fluctuation	2 (0.1)	0	0
Withdrawal of life support	2 (0.1)	0	0
Accident	1 (0.1)	0	0
Autoimmune disorder	1 (0.1)	0	0
Pyrexia	1 (0.1)	0	0
Breast enlargement	1 (0.1)	0	0
Catheter management	1 (0.1)	0	0
Catheter site infection	1 (0.1)	0	0
Catheter site pain	1 (0.1)	0	0
Catheter site related reaction	1 (0.1)	0	0
Dysstasia	1 (0.1)	0	0
Feeling cold	1 (0.1)	0	0
Fluid intake reduced	1 (0.1)	0	0
Food allergy	1 (0.1)	0	0
Impaired quality of life	1 (0.1)	0	0
Transplant rejection	1 (0.1)	0	0
Hyporesponsive To Stimuli	0	0	1 (0.4)
Nail Injury	0	0	1 (0.4)
Propofol Infusion Syndrome	0	0	1 (0.4)
Musculoskeletal-related AEs			
Arthralgia	1 (0.1)	0	0
Foot fracture	1 (0.1)	0	1 (0.4)
Joint surgery	1 (0.1)	0	0
Knee operation	1 (0.1)	0	0
Kyphoscoliosis	1 (0.1)	0	0
Ligament rupture	1 (0.1)	0	0
Lower limb fracture	1 (0.1)	0	0
Meniscus injury	1 (0.1)	0	0
Muscle spasticity	2 (0.1)	0	1 (0.4)
Osteomyelitis	1 (0.1)	0	0
Shoulder fracture	1 (0.1)	0	0
Talipes correction	1 (0.1)	0	0
Tendon operation	1 (0.1)	0	0
Tibia fracture	1 (0.1)	1 (0.1)	1 (0.4)
Muscular weakness	5 (0.3)	0	0
Rheumatoid Arthritis	0	0	1 (0.4)
Osteopenia	0	1 (0.1)	0
Scoliosis	2 (0.1)	0	0
Clavicle fracture	1 (0.1)	0	0
Back pain	1 (0.1)	0	0

Skin-related Suspected AEs			
Petechiae	1 (0.1)	0	0
Pilonidal disease	1 (0.1)	0	0
Wound secretion	1 (0.1)	0	0
Skin disorder	1 (0.1)	0	0
Skin ulcer	2 (0.1)	0	0
Rash	19 (1.1)	5 (4.8)	2 (0.7)
Alopecia	4 (0.2)	0	0
Hypersensitivity	7 (0.4)	0	2 (0.7)
Pruritus	3 (0.2)	0	0
Urticaria	3 (0.2)	0	0
Allergic reaction to excipient	2 (0.1)	0	0
Allergy to vaccine	2 (0.1)	0	0
Erythema	4 (0.2)	1 (1)	0
Skin laceration	2 (0.1)	0	0
Swelling face	2 (0.1)	1 (1)	0
Viral rash	2 (0.1)	0	0
Acne	1 (0.1)	0	1 (0.4)
Blister	1 (0.1)	0	0
Cellulitis	1 (0.1)	0	0
Dermatitis allergic	1 (0.1)	1 (1)	1 (0.4)
Eczema	1 (0.1)	0	0
Flushing	1 (0.1)	0	0
Contusion	0	1 (1)	0
Lymphadenitis	0	1 (1)	0
Subcutaneous abscess	0	1 (1)	0
Respiratory-related Suspected AEs			
Irregular breathing	1 (0.1)	0	0
Lung abscess	1 (0.1)	0	0
Mechanical ventilation	1 (0.1)	0	1 (0.4)
Nasal congestion	1 (0.1)	0	1 (0.4)
Pharyngeal erythema	1 (0.1)	0	0
Pulmonary oedema	1 (0.1)	0	1 (0.4)
Wheezing	1 (0.1)	0	0
Respiration abnormal	1 (0.1)	0	0
Respiratory depression	1 (0.1)	0	0
Respiratory rate increased	1 (0.1)	0	0
Respiratory symptom	1 (0.1)	0	0
Rhinorrhea	1 (0.1)	0	0
Sputum discoloured	1 (0.1)	0	0
Tachypnoea	1 (0.1)	0	0
Tonsillectomy	1 (0.1)	0	0

Tonsillitis	1 (0.1)	0	0
Tracheostomy	1 (0.1)	0	0
Pneumonia	82 (4.9)	4 (3.8)	13 (4.7)
Dyspnoea	19 (1.1)	1 (1)	7 (2.6)
Influenza	17 (1)	0	0
Respiratory distress	16 (0.9)	0	4 (1.5)
Pneumonia aspiration	14 (0.8)	0	5 (1.8)
Oxygen saturation decreased	24 (1.4)	1 (1)	2 (0.7)
Respiratory disorder	12 (0.7)	0	4 (1.5)
Respiratory failure	20 (1.2)	0	0
Nasopharyngitis	11 (0.7)	0	4 (1.5)
Aspiration	10 (0.6)	1 (1)	4 (1.5)
Respiratory syncytial virus infection	9 (0.5)	0	0
Lung Opacity	0	0	1 (0.4)
Acute respiratory failure	7 (0.4)	0	1 (0.4)
Cough	5 (0.3)	2 (1.9)	1 (0.4)
Cyanosis	5 (0.3)	0	0
Acute respiratory distress syndrome	4 (0.2)	0	1 (0.4)
Epistaxis	4 (0.2)	1 (1)	0
Pleural effusion	4 (0.2)	1 (1)	0
Tracheitis	4 (0.2)	0	1 (0.4)
Choking	3 (0.2)	0	2 (0.7)
Chronic respiratory disease	3 (0.2)	0	0
Lung disorder	3 (0.2)	0	0
Pneumonia pseudomonal	3 (0.2)	0	0
Pneumothorax	3 (0.2)	0	1 (0.4)
Respiratory tract infection	3 (0.2)	0	0
Sinusitis	3 (0.2)	0	0
Apnoea	2 (0.1)	0	0
Asthma	2 (0.1)	0	0
Increased bronchial secretion	2 (0.1)	0	0
Increased upper airway secretion	2 (0.1)	0	0
Obstructive airways disorder	2 (0.1)	0	0
Pallor	2 (0.1)	0	0
Pharyngitis	2 (0.1)	0	0
Pneumonitis aspiration	2 (0.1)	0	0
Respiratory arrest	2 (0.1)	0	1 (0.4)
Respiratory tract congestion	2 (0.1)	0	0
Atelectasis	1 (0.1)	0	0
Atypical pneumonia	1 (0.1)	0	0
Bronchiolitis	1 (0.1)	0	0
Bronchitis	1 (0.1)	0	0

Chronic respiratory failure	1 (0.1)	0	0
Dependence on respirator	1 (0.1)	0	0
Hypopnoea	1 (0.1)	0	1 (0.4)
Hypoventilation	1 (0.1)	0	0
Agonal Respiration	0	0	1 (0.4)
Investigations-related AEs			
Alanine aminotransferase increased	6 (0.4)	2 (1.9)	2 (0.7)
Anticonvulsant drug level increased	7 (0.4)	2 (1.9)	1 (0.4)
Antipsychotic drug level increased	2 (0.1)	0	1 (0.4)
Immunosuppressant Drug Level Increased	0	0	2 (0.7)
Aspartate aminotransferase increased	4 (0.2)	2 (1.9)	1 (0.4)
Platelet count decreased	2 (0.1)	4 (3.8)	3 (1.1)
Blood bilirubin increased	8 (0.5)	4 (3.8)	1 (0.4)
Drug level increased	5 (0.3)	1 (1)	1 (0.4)
Hypoglycaemia	4 (0.2)	0	1 (0.4)
Neutropenia	2 (0.1)	1 (1)	1 (0.4)
Blood calcium increased	0	1 (1)	1 (0.4)
Leukopenia	0	0	1 (0.4)
Hyperglycemia	0	0	1 (0.4)
WBC count increase	0	0	1 (0.4)
Hepatobiliary system-related AEs			
Liver injury	3 (0.2)	2 (1.9)	1 (0.4)
Portal shunt	1 (0.1)	0	0
Cholelithiasis	2 (0.1)	2 (1.9)	0
Hepatic cytolysis	2 (0.1)	0	0
Hepatitis fulminant	2 (0.1)	0	0
Metastases to liver	2 (0.1)	0	0
Hepatic enzyme abnormal	1 (0.1)	0	0
Hepatic failure	1 (0.1)	1 (1)	2 (0.7)
Splenomegaly	1 (0.1)	0	0
Excretory and reproductive system-related AEs			
Pollakiuria	1 (0.1)	0	0
Renal failure	1 (0.1)	0	0
Urinary bladder haemorrhage	1 (0.1)	0	0
Urinary incontinence	2 (0.1)	1 (1)	2 (0.7)
Urine cannabinoids increased	1 (0.1)	0	0
Urine odour abnormal	1 (0.1)	0	0
Urine output increased	1 (0.1)	0	0
Urinary retention	5 (0.3)	1 (1)	2 (0.7)
Nephrolithiasis	4 (0.2)	0	2 (0.7)
Urine output decreased	3 (0.2)	0	1 (0.4)
Renal disorder	2 (0.1)	0	1 (0.4)

Renal transplant	2 (0.1)	0	0
Urine abnormality	2 (0.1)	0	1 (0.4)
Amenorrhoea	1 (0.1)	0	0
Bladder irritation	1 (0.1)	0	0
Blood urea increased	1 (0.1)	0	0
Chromaturia	1 (0.1)	0	1 (0.4)
Ovarian Cyst Ruptured	0	0	1 (0.4)
Priapism	0	1 (1)	0
Adenoidectomy	0	0	1 (0.4)
Infections			
Adenovirus infection	1 (0.1)	0	0
Bacterial infection	1 (0.1)	0	0
Staphylococcal cellulitis	1 (0.1)	0	0
Citrobacter infection	1 (0.1)	0	0
Clostridium difficile infection	1 (0.1)	0	1 (0.4)
Coronavirus infection	3 (0.2)	0	1 (0.4)
Ear infection	4 (0.2)	0	1 (0.4)
Enterovirus infection	3 (0.2)	0	1 (0.4)
Escherichia infection	3 (0.2)	0	0
Gastroenteritis viral	8 (0.5)	0	1 (0.4)
Gastrointestinal infection	2 (0.1)	0	0
Infected cyst	1 (0.1)	0	0
Infection	8 (0.5)	0	3 (1.1)
Infectious mononucleosis	1 (0.1)	0	0
Infective pulmonary exacerbation of cystic fibrosis	1 (0.1)	0	0
Viral influenza	1 (0.1)	0	2 (0.7)
Kidney infection	1 (0.1)	0	0
Lower respiratory tract infection	2 (0.1)	0	0
Metapneumovirus infection	2 (0.1)	0	2 (0.7)
Moraxella infection	1 (0.1)	0	1 (0.4)
Norovirus infection	1 (0.1)	0	0
Parainfluenza virus infection	3 (0.2)	0	0
Streptococcal pharyngitis	1 (0.1)	0	2 (0.7)
Pneumonia bacterial	5 (0.3)	0	1 (0.4)
Pneumonia klebsiella	1 (0.1)	0	0
Pneumonia respiratory syncytial viral	1 (0.1)	0	0
Pneumonia viral	1 (0.1)	0	1 (0.4)
Postoperative wound infection	1 (0.1)	0	0
RSV infection	1 (0.1)	0	2 (0.7)
Rhinovirus infection	13 (0.8)	0	2 (0.7)
Sepsis	10 (0.6)	0	1 (0.4)

Septic shock	2 (0.1)	0	2 (0.7)
Serratia test positive	1 (0.1)	0	1 (0.4)
Staphylococcal infection	3 (0.2)	0	0
Stoma site infection	1 (0.1)	0	0
Streptococcal infection	2 (0.1)	0	0
Superinfection bacterial	2 (0.1)	0	0
Upper respiratory tract infection	5 (0.3)	0	1 (0.4)
Urinary tract infection pseudomonal	1 (0.1)	0	0
Urinary tract infection	26 (1.5)	o	O
Urosepsis	1 (0.1)	0	0
Viral diarrhoea	1 (0.1)	0	0
Viral infection	16 (0.9)	0	1 (0.4)
Pseudomonas wound infection	1 (0.1)	0	0
Varicella infection	0	1 (1)	0
Skin infection	0	1 (1)	0
Viral respiratory infection	0	0	1 (0.4)
Cardiovascular system-related AEs			
Myocardial infarction	1 (0.1)	0	0
Oedema peripheral	1 (0.1)	0	0
Tachycardia	2 (0.1)	0	0
Cardiac arrest	8 (0.5)	0	4 (1.5)
Hypotension	4 (0.2)	0	1 (0.4)
Cardiac disorder	2 (0.1)	0	0
Heart rate increased	2 (0.1)	0	0
Hypertension	3 (0.2)	0	2 (0.7)
Angioedema	1 (0.1)	0	0
Arrhythmia	1 (0.1)	0	0
Haemodynamic Instability	0	0	1 (0.4)
Bradycardia	1 (0.1)	0	0
Cardiac failure	1 (0.1)	0	1 (0.4)
Blood pressure abnormal	1 (0.1)	0	0
Coagulopathy	1 (0.1)	0	0
Disseminated intravascular coagulation	1 (0.1)	0	0
Heart rate abnormal	1 (0.1)	0	0
Heart rate decreased	1 (0.1)	0	0
Eye and ear related			
Eye swelling	3 (0.2)	0	0
Otorrhoea	1 (0.1)	0	0
Pupil fixed	1 (0.1)	0	0
Pupillary reflex impaired	1 (0.1)	0	0
Mydriasis	5 (0.3)	0	0
Eye movement disorder	2 (0.1)	0	0

Ocular hyperaemia	2 (0.1)	0	0
Vision blurred	2 (0.1)	0	0
Blepharospasm	1 (0.1)	0	0
Conjunctivitis	1 (0.1)	0	0
Ear pain	1 (0.1)	0	0
Ear tube insertion	1 (0.1)	0	0
Eye injury	1 (0.1)	0	0
Eyelid Function Disorder	0	0	1 (0.4)

eTable 3.4. Negative signals for adverse events associated with CBD as a primary suspect.

Adverse events (AEs)	n	PRR 95% CI	ROR 95% CI	Chi-square with Yate's correction
CNS-related AEs				
Somnolence	30	1.57 (1.11-2.24)	1.60 (1.11-2.29)	5.78
Lethargy	9	1.43 (0.74-2.74)	1.43 (0.74-2.76)	0.76
Insomnia	9	0.86 (0.45-1.65)	0.86 (0.44-1.65)	0.09
Hypersomnia	7	1.76 (0.57-5.46)	1.76 (0.56-5.48)	0.37
Tremor	4	0.45 (0.17-1.21)	0.45 (0.17-1.21)	2.13
Sleep disorder	1	0.20 (0.03-1.44)	0.20 (0.03-1.44)	2.39
Pain	4	0.31 (0.12-0.82)	0.31 (0.11-0.82)	5.61
Abnormal behaviour	7	0.55 (0.26-1.15)	0.55 (0.26-1.15)	2.18
Ataxia	1	0.47 (0.07-3.30)	0.47 (0.07-3.31)	0.20
Aggression	12	0.88 (0.50-1.53)	0.87 (0.49-1.54)	0.12
Irritability	4	0.46 (0.17-1.22)	0.46 (0.17-1.22)	2.06
Agitation	8	0.75 (0.37-1.49)	0.75 (0.37-1.50)	0.46
Anxiety	4	0.28 (0.11-0.75)	0.28 (0.10-0.74)	6.77
Balance disorder	1	0.63 (0.09-4.50)	0.63 (0.09-4.50)	0.01
Asthenia	3	0.42 (0.14-1.30)	0.42 (0.13-1.30)	1.89
GI-related AEs				
Vomiting	21	0.53 (0.35-0.81)	0.52 (0.34-0.80)	8.68
Diarrhea	20	1.13 (0.73-1.74)	1.13 (0.72-1.76)	0.17
Drooling	3	3.09 (0.99-9.59)	3.093 (0.99-9.65)	2.38
Feeding disorder	3	3.16 (1.02-9.81)	3.16 (1.01-9.87)	2.51
Abdominal pain upper	3	0.28 (0.09-0.87)	0.28 (0.09-0.86)	4.92
Constipation	7	1.48 (0.71-3.10)	1.49 (0.71-3.13)	0.67
Nausea	5	0.21 (0.09-0.50)	0.20 (0.08-0.49)	14.87
Abdominal pain	3	0.19 (0.06-0.60)	0.19 (0.06-0.60)	9.42
Pancreatitis	4	1.57 (0.59-4.18)	1.57 (0.59-4.20)	0.35
Abdominal discomfort	3	0.76 (0.25-2.36)	0.76 (0.25-2.37)	0.05
Dehydration	5	1.02 (0.42-2.44)	1.02 (0.42-2.45)	0.04
Fatigue	19	1.10 (0.71-1.73)	1.11 (0.70-1.74)	0.10
Death	176	14.07 (12.28-16.13)	16.87(14.31-19.90)	2081.15
Pyrexia	12	0.36 (0.21-0.64)	0.357 (0.20-0.63)	13.12
Weight decreased	17	1.53 (0.95-2.45)	1.54 (0.95-2.49)	2.62
Hospitalization	127	30.83 (26.03-36.51)	35.18 (29.03-42.64)	3399.03
Rash	9	0.41 (0.21-0.78)	0.40 (0.21-0.78)	7.28
Hypersensitivity	2	0.25 (0.06-0.99)	0.25 (0.06-0.99)	3.81
Pruritus	3	0.20 (0.06-0.61)	0.19 (0.06-0.61)	9.15
Respiratory system				
Dyspnoea	8	0.49 (0.25-0.98)	0.49 (0.24-0.98)	3.79
Influenza	6	1.15 (0.52-2.56)	1.15 (0.52-2.57)	0.02
Respiratory distress	2	0.96 (0.40-2.31)	0.96 (0.40-2.31)	0.02
Oxygen saturation decreased	5	1.06 (0.44-2.54)	1.06 (0.44-2.55)	0.11
Respiratory failure	7	1.09 (0.52-2.29)	1.09 (0.52-2.30)	0.11

Acute Respiratory failure	3	2.77 (0.90-8.61)	2.78 (0.90-8.65)	1.84
Cough	6	0.49 (0.22-1.10)	0.50 (0.22-1.09)	2.67
Nasopharyngitis	11	1.73 (0.96-3.11)	1.73 (0.96-3.11)	2.68
Dysphagia	4	0.98 (0.37-2.61)	0.98 (0.37-2.62)	0.04
Alanine aminotransferase increased	3	0.54 (0.17-1.67)	0.54 (0.17-1.68)	0.76
Aspartate aminotransferase increased	2	0.40 (0.10-1.60)	0.40 (0.10-1.60)	1.26
Thrombocytopenia	2	0.32 (0.08-1.28)	0.319 (0.08-1.28)	2.26
Neutropenia	2	0.24 (0.06-0.97)	0.242 (0.06-0.97)	4.01
Leukopenia	1	0.35 (0.05-2.52)	0.35 (0.05-2.52)	0.62
Liver injury	1	0.60 (0.085-4.28)	0.602 (0.085-4.286)	0.015
Cholelithiasis	1	0.43 (0.06-3.08)	0.43 (0.06-3.08)	0.28
Urinary retention	4	2.41 (0.91-6.44)	2.42 (0.90-6.48)	2.039
Urine output decreased	1	1.368 (0.19-9.74)	1.37 (0.19-9.76)	0.073
Infection	8	1.49 (0.75-2.98)	1.50 (0.74-3.01)	0.85
Respiratory syncytial virus infection	6	1.78 (0.80-3.95)	1.78 (0.797-3.98	1.33
Clostridium difficile infection	1	1.01 (0.14-7.17)	1.01 (0.14-7.19)	0.24
Sepsis	1	0.18 (0.03-1.30)	0.18 (0.03-1.29)	2.92
Septic shock	1	0.40 (0.06-2.80)	0.39 (0.05-2.80)	0.42
Upper respiratory tract infection	3	1.10 (0.36-3.42)	1.10 (0.36-3.43)	0.02
Urinary tract infection	12	4.23 (2.40-7.45)	4.27 (2.41-7.58)	26.26
Pneumonia bacterial	1	2.92 (0.41-20.85)	2.922 (0.41-20.91)	0.07
Viral respiratory infection	3	3.10 (0.20-9.64)	3.108 (0.20-9.70)	2.41
Cardiac arrest	9	1.33 (0.70-2.55)	1.33 (0.69-2.57)	0.44
Hypotension	1	0.09 (0.012-0.60)	0.08 (0.01-0.60)	9.12
Hypertension	3	0.43 (0.14-1.34)	0.43 (0.14-1.36)	1.72
Eye swelling	1	0.42 (0.06-2.98)	0.42 (0.060-2.97)	0.33

eTable 3.5. Characteristics of the included studies, participants, and drug interactions.

Author, Year	Country	Study design	Duration of treatment	No of patient, n (%) female, Age (yr)	Indication of cannabinoids	Cannabinoids administered, Dose, Route	Concomitant drugs	Interacting drugs	Type of interaction	Drug interaction findings	Outcomes	Safety outcomes
Case reports												
Wiemer-Kruel 2019 (41)	Single centric, Germany	Case report	6 weeks	1, 1 (100), 6.5	TSC	Purified CBD, 500 mg/day	CBD, EVE, LTG, LAC	CBD and EVE	PK	CBD increased plasma concentration of EVE from 4 -5 µg/L to 12-16 µg/L	N/A	N/A
Madden 2020 (38)	Single centric, US	Case report	N/A	1, 1 (100), 13	Neuroendocrine tumor	5 mL of CBD oil (25 mg/mL) by mouth TDS, for the last 2 months followed by 5ml of CBD oil 50 mg/ml	Methadone	Methadone	PK	CBD increased plasma levels of methadone, methadone levels with after CBD administration 271 ng/mL, followed by 147 ng/ml and 125 ng/mL after cessation of CBD on day 7 and day 14, respectively	N/A	Fatigue score 4/4, 2/4, and 1/4 on day 1, day 7 and day14 after CBD cessation, respectively
Ortenzi 2020 (39)	Single centric; Italy	Case report	N/A	1,1 (100), 17	Dravet syndrome	purified CBD, 5-15 mg/kg/ day	VPA, CLB, STP	VPA	PK	CBD increased plasma concentration of VPA to 129.7 microg/mL	N/A	Decrease in platelet count to 98×10000 /mmc and elevation in AST 151 U/L, ALT 45 U/L

Singh 2020 (40)	Single centric, US	Case report	N/A	1, 0, 13	ASD and Lennox-Gastaut syndrome	CBD 5 mg/kg/day to 10 mg/kg/day	Lithium 600 mg qAM, 300 mg qPM and 600 mg qhs, Perphenazine 8 mg TID, Quetiapine 200 mg twice a day and 400 mg qhs, and Trazodone 300 mg qhs CLB, 0.5 mg/kg/day.	Lithium and CLB	PK	CBD increase plasma concentration of lithium (1 -1.3 mmol/L to 2.4 mmol/L)	N/A	Patient developed hypersomnolence, ataxia, tired, lethargic, off-balance unsteadiness, and decreased oral intake following CBD administration
Case series												
Anderson 2022 (42)	Single centric, Australia	Case series	N/A	2, 0, 17 and 41	ASD	purified CBD, CHE (CBD THC 11)	CBD and fluoxetine, clonidine, and other	CBD and Fluoxetine	PK	Patient had null CYP2D6 variant, as a result CBD increased the plasma concentration of Fluoxetine	N/A	N/A
Geffrey 2015 (44)	Single centric, US	Case series	8 weeks	13, 6 (46.1), mean 11 (range 4-19)	DRE	purified CBD, 5 mg/kg/day to 25 mg/kg/day (5 mg/kg/day	CLB, VPA, rufinamide, phenytoin, LAC, LEV, felbamate, ZNS,	CLB	PK	CBD increased concentration of CLB, mean increase in CLB levels was 60 ± 80%, mean increase in nCLB levels was 500 ± 300% (95% CI	>50% reduction in seizure frequency n= 9/13 (69.2)	Side effects were reported in 10 (77%) of the 13 subjects but were alleviated with CLB dose reduction.

						increment)	vigabatrin, lamotrigine			[+90–610%] at week 8. 1.9 times increase in n-CLB levels		
Klotz 2019 (45)	Single centric, Germany	Case series	N/A	5, 1 (20), mean 24.6 (range 10-54)	DRE	purified CBD, 5 to 20-50 mg/kg/day	Phenobarbital, LTG, LAC, Perapamil, Pregabalin, CLB	BRV	PK	CBD increased plasma levels of BRV by 95% to 280%, mean plasma levels for BRV 150 mg, and 300 mg after CBD were 4240 ± 850, and 8580 ± 1360	Mean change in seizure frequency 43.9 (-18.6 to -72.5)	adverse event occurred in 2/5 (diarrhea and somnolence) patients
Potey 2022 (46)	Single centric, France	Case series	N/A	3, 1 (25), median 6	Lennox-Gastaut syndrome, DRE, dravet syndrome	purified CBD, N/A	CLB	CLB	PK	CBD increased n-CLB levels in three patients (6340microg/l), median CBZ/n-CLB ratio 2.2, CBD and CLB plasma levels were normal	N/A	Hospitalization due to muscular hypotonia, lengthened sleep, anorexia, and weight loss in two patients, another patient was asymptomatic
Cáceres Guido 2020 (43)	Single centric, Argentia	Case series	21 days	12, 10 (83.3), median (range) 10.2 (2.5-17.2)	DRE	purified CBD, median (range) 12.2 (5.3-19.4)	AEDs, and levothyroxine	Levothyroxine	PK	Levothyroxine increased CBD's C0/D (median 34.5 ng/mL/mg/kg, range 22.3-46.7 vs 37.3 ng/mL/mg/kg range 28.8-45.9) and Cmax/D (4.9 ng/mL/mg/kg range 2.5-15.2 vs 9.7 ng/mL/mg/kg range 5.4-17.2)	N/A	N/A
Observational studies												

Wang 2020 (54)	Single centric, US	Prospective observational study	152 weeks	29, mean ± sd 9.7±4.3	DRE	CBD-enriched CHE, 2.5 to 199 mg CBD or 0.13 to 5.0 mg/kg	LEV, ZNS, CLB, rufinamide, felbamate, LTG, valproic acid, TPM, clonazepam, pregabalin, oxcarbazepine, LAC, phenobarbital, and midazolam	LEV and ZNS	PK	ZNS (n=3 patients) AUC significantly decreased elimination rate constant (Ke) of CBD and increased covariate parameters (V1); inactive LEV (n=5) carboxylic acid metabolite decreased Ke of CBD	N/A	N/A
Sabus 2024 (52)	Single centric, US	Retrospective chart review	2-4 months	3, N/A, range 17-18	TSC and SEGA	purified CBD, N/A	CBD and EVE	CBD and EVE	PK	CBD treatment for 2-4 months increased the EVE trough concentration by 200-860% beyond the normal value	N/A	One patient reported new-onset involuntary movements
Ebrahimi-Fakhari 2019 (50)	Single centric, US	Retrospective chart review	N/A	25, 7 (28), median 17 (range 3-45)	Tuberous Sclerosis Complex	purified CBD, 5-20 mg/kg/day	ERV, SRL and antiepileptic drugs	EVE, SRL	PK	CBD increased plasma levels of mTOR inhibitors, mean change in EVE from baseline +9.8 ng/mL and SRL + 5.1 ng/mL	N/A	Adverse events occurred in n=10/25, 40% of patients, no serious adverse events
McNamara 2020 (51)	Single centric, US	Retrospective	8 months	87, 43 (49), mean	DRE	purified CBD, 13.6 ±	VPA	VPA	PD	Risk of thrombocytopenia (PLT range 17	N/A	Increase in ALT, AST levels and

		chart review		9.8 (1.2-19.8)		5.0 mg/kg/day				000-108 000/μL) in 9/23 patients on CBD and VPA and elevation in ALT and AST levels		decrease in PLT counts
Knupp 2019 (53)	Single centric, US	Observational	12 weeks	21, 8 (38), median (range) 10.3 (6.8-12.6)	DRE	CBD-enriched CHE, median (range) 0.9 (0.6–2.2) mg/kg/day	TPM, CLB, VPA and other AEDs	Increase in n-CLB (n= 2/3), TPM (n=1/2) and VPA levels (n=3/3)	PK	CBD increases plasma levels of n-CLB, TPM, and VPA	>50% reduction in seizure n=5/21 (24)	N/A
Interventional studies												
Gaston 2017 (48)	NA	Open label single arm study		81, 40 (49.3) Pediatric arm mean 10.4 (range 2-19), Adult arm mean 29.1 (range 19-62)	DRE	purified CBD, 5 mg/kg/day to 50 mg/kg/day (5 mg/kg/day increment)	CLB/n-CLB, VPA, LEV, Phenobarbital, Clonazepam, Phenytoin, Carbamazepine, LTG, Oxcarbazepine, Ethosuximide,	CLB/n-CLB, ZNS, TPM, Eslicarbazepine, Rufinamide	PK	CBD led to increase in levels of n-CLB (2,207.5 ± 1854 ng/ml vs 3,696.8 ± 1,027.1 ng/ml), Eslicarbazepine (14.4 ±7.4 vs 17.8 ± 9.1 μg/ml), TPM (10.3 ± 5.9μg/ml vs 11.3 ± 8.3μg/ml), ZNS (17.2 ± 12.2μg/ml vs 42) Rufinamide (24.8	NA	Significant effect on VPA dose on both AST (p = 0.002) and ALT (p = 0.023) in all patients and within both pediatric and adult arm; Mean ALT levels (VPA vs other AEDs) 35.3 U/L vs 23.7 U/L and AST 37.1 u/l

							TPM, Vigabatrin, ZNS, Eslicarbazepine, Ezogabine, Pregabalin, Perampanel, Rufinamide, LAC			± 12.8 vs 27 ± 14.7 µg/ml)		vs 23.97 U/L; Sedation in CLB plus CBD group Adults 6/12 and Children 8/15
Wheless 2019 (49)	Multicentric, US	Non-randomized single arm study	Treatment 11 days, follow-up 11-17 days	61, 28 (45.9), mean± sd 7.6 ±5.2	DRE	purified CBD, 5-40 mg/kg/day	CLB	CBD and CLB	Bidirectional PK	On day 10, CLB increased CBD concentration (n=32, 52.5) 2.5 times, 7-OH CBD 3.06 times compared with patients not on CLB as well as 1.7- and 2.2 times increase in CLB in patients, 1.3- and 1.9-fold increase in n-CLB on 10mg/kg/CBD and 40 mg/kg/CBD, respectively	N/A	7 patients reported somnolence (n=32 patients on CBD and CLB)
Gaston 2019 (47)	Single centric, US	Open-label single arm interventional study	48 weeks	132, mean ± sd 9.5 ± 12.9	Epilepsy (Partial and Generalised seizures)	purified CBD, 5 mg/kg/day to 50 mg/kg/day (5 mg/kg/	CBD, CLB, and other AEDs	CLB	PK	Independent of coadministration of CLB, no differences in treatment response were observed (all P < 0.05).	Seizure frequency and severity, no changes observed	N/A

						day increment)						
Devinsky 2018 (56)	Multicentric, US and UK	RCT	4 weeks	34, 18 (53) mean ± sd 7.6 ± 1.8	Dravet syndrome	Purified CBD 5, 10,20 mg/kg/d	CLB, LEV, STP, TPM, AND VPA	CLB, STP, and VPA	PK	CBD increased plasma concentration n-CLB (≥166% increase)	N/A	Treatment-emergent AEs 5 mg CBD/kg/d 8/10 (80%), 10 mg CBD/kg/d—5/8 patients (63%); 20 mg CBD/kg/d 7/9 (78%), placebo 6/7 (86%)
Ben Menachem 2020 (55)	Multicentric, Spain, the Netherlands and Sweden	RCT	26 days	34, 12 (35), mean ±sd 29.5 ± 10.5	DRE	purified CBD, 20 mg/kg/day	VPA and STP	VPA and STP	PK	CBD led to increase in plasma concentration (Cmax) of STP by 17%, increase in area under the concentration–time curve over the dosing interval by 30%; CBD led to 30% decrease in VPA Cmax	N/A	Serious adverse event STP arm 1/12 (8%), VPA arm 1/16 (6%)

Abbreviations BRV Brivaracetam, CLB Clobazam, SRL Sirolimus, TDS Three times a day, TSC Tuberous Sclerosis Complex, TPM Topiramate, EVE Everolimus, LEV Levetiracetam, LAC Lacosamide, N/A Not available, PK Pharmacokinetic, PD Pharmacodynamic, VPA Valproic acid, ZNS Zonisamide

3.13.3 Search Strategy

3.13.3.1 Multifile Ovid Search

Embase <1974 to 2021 June 16>
Ovid MEDLINE(R) ALL <1946 to June 16, 2021>
APA PsycInfo <1806 to June Week 1 2021>

1 Cannabis/

2 exp Cannabinoids/

3 Cannabaceae/

4 Medical Marijuana/

5 Marijuana Use/

6 Marijuana Smoking/

7 cannab*.tw, kf.

8 Mari?uana*.tw, kf.

9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw, kf.

10 (19GBJ60SN5 or 2N4O9L084N or 7J8897W37S or K4H93P747O).rn.

11 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw, kf.

12 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw, kf.

13 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw, kf.

14 or/1-13 [CANNABIS CONCEPT]

15 exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or

newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn. [CHILDREN CONCEPT]

16 14 and 15

17 exp Animals/ not (exp Animals/ and Humans/)

18 16 not 17 [EXCLUDING ANIMAL ONLY STUDIES]

19 (202106* or 202107* or 202108* or 202109* or 20211* or 2022*). dt, ez, da.

20 18 and 19

21 20 use medall

22 cannabis/

23 exp cannabinoid/

24 cannabaceae/

25 exp "cannabis (genus)"/

26 medical cannabis/

27 exp "cannabis use"/

28 cannab*.tw, kw.

29 Mari?uana*.tw, kw.

30 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw, kw.

31 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw, kw.

32 (8063-14-7 or 1972-08-3 or 13956-29-1 or 51022-71-0 or 8001-54-5 or 33086-25-8 or 36557-05-8 or 24359-49-7).rn.

33 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw, kw.

34 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw, kw.

35 or/22-34

36 exp child/ or exp newborn disease/ or exp infant/ or exp adolescent/ or exp pediatrics/ or abandoned child/ or gifted child/ or orphaned child/ or unwanted child/ or "minor (person)"/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

37 35 and 36

38 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

39 Animal experiment/ not (human experiment/ or human/)

40 38 or 39

41 37 not 40

42 limit 41 to dc=20210617-20220427

43 42 use oemezd

44 exp cannabis/

45 exp cannabinoids/

46 marijuanas/

47 marijuana usage/

48 marijuana legalization/

49 cannab*.tw.

50 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla).tw.

51 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw.

52 (epidiolex or gwp 42003p or gwp42003p or nabidiolex).tw.

53 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726").tw.

54 or/44-53 [Cannabis Concept]

55 limit 54 to (childhood <birth to 12 years> or adolescence <13 to 17 years>)

56 exp pediatrics/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.

57 54 and 56

58 55 or 57

59 exp Animals/ not (exp Animals/ and Humans/)

60 58 not 59

61 60 use psyc17

62 60 use psyc18

63 60 use psyc16

64 or/61-63

65 21 or 43 or 64

66 remove duplicates from 66

**Note Ovid multifile search of MEDLINE, Embase, and PsycInfo were run on June 20, 2020, June 17, 2021, April 27, 2022, and April 24, 2023. The search remains unchanged except for date limits.*

3.13.3.2 Cochrane Library (Wiley) Search Strategy

ID Search

#1 MeSH descriptor [Cannabis] this term only

#2 MeSH descriptor [Cannabinoids] explode all trees

#3 MeSH descriptor [Cannabaceae] this term only

#4 MeSH descriptor [Medical Marijuana] this term only

#5 MeSH descriptor [Marijuana Use] explode all trees

#6 MeSH descriptor [Marijuana Smoking] this term only

#7 cannab* ti, ab, kw

#8 Mari? uana* ti, ab, kw

#9 (bhang* or ganja* or ganjah or hash or hashish or hemp* or charas or sinsemilla) ti, ab, kw

#10 (dronabinol or marinol or thc or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9tetrahydrocannabinol* or "Delta (9) tetrahydrocannabinol" or tetrahydrocannabivarin or cesamet or nabilone or nabiximols or dexanabinol or sativex or "hu 211" or hu211 or "hu 210" or hu210 or deltanyne or cannador* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex) ti, ab, kw

#11 (deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726") ti, ab, kw

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 MeSH descriptor [Child] explode all trees

#14 MeSH descriptor [Congenital, Hereditary, and Neonatal Diseases and Abnormalities] explode all trees

#15 MeSH descriptor [Infant] explode all trees

#16 MeSH descriptor [Adolescent] this term only

#17 MeSH descriptor [Pediatrics] explode all trees

#18 MeSH descriptor [Child, Abandoned] this term only

#19 MeSH descriptor [Child, Exceptional] this term only

#20 MeSH descriptor [Child, Orphaned] this term only

#21 MeSH descriptor [Child, Unwanted] this term only

#22 MeSH descriptor [Minors] this term only

#23 (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or "premature birth*" or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or "elementary school*" or "nursery school*" or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*)ti, ab, kw

#24 (child* or adolesc* or pediat* or paediat*)so

#25 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

**Note Cochrane Library search via Wiley were run on June 20, 2020, June 17, 2021, April 27, 2022, and April 24, 2023. The search remained unchanged except for date limits and a correction in a typo between June 2020 and June 2021 in Line #11 where ti, ab, kw was used instead of ti, ab, kw*

Chapter 4 Overall conclusion and future research directions

4.1 General conclusions

As global medical cannabis regulations and laws have evolved over the past decade, both interest and research on the use of cannabinoids for medical purposes in children have expanded rapidly.(1) This thesis synthesizes current evidence on the safety of cannabinoids used for medical purposes in children by integrating evidence from existing studies and a review of cannabidiol (CBD)-related spontaneous reports. Identified studies reported an increase in cannabinoid use in children with drug-resistant epilepsies, cancer, autism spectrum disorder, and other complex health illnesses. Robust evidence gaps exist related to the long-term safety, benefits, dosing, tolerability, and drug interactions of cannabinoids in children with these conditions.(1-3)

To begin to fill these gaps, we synthesized the frequency and type of adverse events related to cannabinoid use for medical purposes in children reported in randomized controlled trials (RCTs). Cannabinoid use for medical purposes were associated with an increased risk of adverse events, serious adverse events, and withdrawals due to adverse events compared with controls. Additionally, we reviewed Cannabidiol (CBD)-related spontaneous reports and generated signals for CBD-related adverse events such as somnolence, lethargy, seizures, sudden unexplained death, death, hospitalization, and falls.

CBD was reported to interact with clobazam, valproic acid, mTOR inhibitors (everolimus and sirolimus), topiramate, zonisamide, methadone, lithium, brivaracetam, fluoxetine, levothyroxine, levetiracetam, stiripentol, rufinamide, and eslicarbazepine. Findings from this thesis will provide insights to guide future clinical research on cannabinoid use for medical purposes in children and current clinical practice in the absence of rigorous evidence.

Many different cannabis-based medicines were identified across a wide range of indications. Purified CBD and CBD-enriched cannabis herbal extracts (commonly high CBD and low THC) were used in children with drug-resistant epilepsies and autism spectrum disorder.(2) Nabilone, dronabinol (synthetic THC), and CBD-enriched cannabis herbal extracts were used for symptom management in children with cancer.(3) Purified CBD was the most commonly used cannabinoid for medical purposes in children. It was reported to be tolerable in children up to a maximum dose of 20 mg/kg/day. However, compared to placebo, an increased risk of adverse events was reported with CBD.(2, 4) The long-term safety studies on CBD remain limited across many indications, with a exception of a study, where follow-up duration was up to 144 weeks in children with drug-resistant epilepsy.(5) We identified various indications specifically, inflammatory bowel disease,(6, 7) multiple sclerosis,(8, 9) epidermal bullosa,(10) dysautonomic syndrome,(11) Rett syndrome,(12) and cystic fibrosis,(13) where cannabinoids were used in children in single-patient case reports and small case series but lacked interventional studies, especially RCTs. Further, the safety and effectiveness evidence on adding THC to CBD-enriched cannabis herbal extracts in children with DRE comes from a small case series(14) or single-arm studies.(15-18) The small and uncontrolled nature of these studies limit the strength of evidence to inform practice guidelines. The lack of high-quality evidence on cannabinoid dosing, safety, and effectiveness in children highlights an urgent need to conduct high-quality randomized controlled trials and rigorous observational studies.

One indication where cannabinoid use has been identified includes managing symptoms associated with pediatric cancer and cancer treatments. In section 2.2, we have summarized cannabinoid use in children with cancer; cannabinoids have been used in children with cancer for symptom management, such as chemotherapy-induced nausea and vomiting, pain, tumor-related

convulsions, and anorexia.(3) However, there are evidence gaps related to cannabinoid product selection, doses, safety, and drug interaction in children with cancer. They may be beneficial for symptom management in children with cancer. However, their use is not yet supported by high-quality evidence, which makes creating clinical recommendations to provide optimal care and support for these families challenging. There is a need to conduct multijurisdictional randomized controlled trials evaluating the safety and efficacy of cannabinoids for symptom management in children with cancer. Studies should consider studying the specific cannabis products that are available in their jurisdictions for clinical trials, with pre-planned synthesis efforts from international teams.

An additional potential indication for medical cannabis in children, where there are currently limited effective treatment options, is autism spectrum disorder. In section 2.3, we reported an increase in interest and research on cannabinoid use in children with ASD. Identified studies reported that parents access cannabinoids with or without authorization from their healthcare practitioners for symptom management in their children with ASD. Cannabinoids may improve aggression, epilepsy, behavioral problems, cognition, hyperactivity, anxiety, irritability, and sleep in children with ASD.(19) Outcome assessment tools used in cannabinoid-related ASD studies in children were subjective and lacked reliability and validity, which makes it challenging to compare and combine data from across studies. We highlight the need for high-quality evidence on the safety, effectiveness, and tolerability of cannabinoids in children with ASD.

For the few identified clinical trials that have been conducted and included pediatric patients, we reported that cannabinoids were associated with an increased risk of adverse events, withdrawals due to adverse events, and serious adverse events (section 2.4). Somnolence, diarrhea, lethargy, and elevation in transaminase levels were commonly reported adverse events

with higher risk ratios.(20) Cannabinoids have the potential to interact with other chemical entities, especially CBD, which has a strong ability to interact with clobazam, sodium valproate, and benzodiazepines.(21) There were very few clinical trials on cannabis extracts in the included studies that did not show the same increase in adverse events that were seen in studies on CBD isolates. Physicians and caregivers of children receiving cannabinoids should continue to follow the Canadian Pediatric Society's statement on medical cannabis, which includes being vigilant and monitoring for any adverse events and cannabinoid-related drug interactions.

To better understand what cannabinoids associated with adverse events are reported in the real world, chapter 3 of this thesis maps CBD's real-world adverse event profile from spontaneous reports using data from the FDA adverse event reporting system (FAERS) and EudraVigilance. We identified signals for adverse events associated with CBD isolates, namely seizures, sudden unexplained death, death, hospitalization, and falls. Additionally, we reported a higher prevalence of infections in children taking CBD isolates, such as pneumonia and viral infections. Globally, access to cannabis products looks very different. While jurisdictional regulations prohibit cannabis sales directly to children, cannabis products from the recreational and illicit markets that do not have accurate product labels create additional challenges with interpreting evidence due to challenges in quantifying cannabis exposures. The quantity of CBD, THC, and other active compounds in unlicensed products should be reported, as well as the route of administration and frequency of dosing, but there is no standard currently to do so, and no Drug Identification Number is available for tracking medical cannabis in administrative health data.

CBD interactions with other drugs create an increased risk of developing unwanted effects and even therapeutic failure.(21) Coadministration of CBD with valproic acid increased

liver transaminase levels and decreased platelet count in children.(22-25) When CBD was administered with clobazam, adverse events, including somnolence, sedation, lethargy, and fatigue, were reported.(26) These findings underscore the value of adverse event monitoring in children on CBD and tailoring their therapeutic regimen individually to mitigate the risk of interactions. This is especially relevant and important for children with complex health concerns who may be taking multiple medications each day.

Data generated from my current work, which involves a review of CBD-related spontaneous reports, drug interaction literature, and studies cited below, supports the Canadian Pediatric Society's current statement that pediatricians should be vigilant while monitoring children receiving both CBD and clobazam for adverse events. Particularly, they should monitor for adverse events such as somnolence, lethargy, fatigue, and dizziness.(26) All these studies demonstrated a lack of assessment of long-term outcomes, which hindered our ability to evaluate the impacts of cannabinoid use for medical purposes on neurodevelopment in children.(1) Acknowledging that multidisciplinary teams and long-term funding strategies will be needed to generate this evidence, pediatricians should be prepared to have open discussions with parents about the limited evidence on the long-term safety of cannabinoid use for medical purposes in children.

Studies identified in this thesis exploring cannabinoids used for medical purposes lack standard efficacy and safety outcome assessment tools, hindering our ability to interpret findings across studies. The indication-specific outcome assessment tools used in identified studies, except epilepsy, were highly subjective and lacked internal validity and reliability. This limited our ability to supplement evidence synthesis with indication-specific efficacy outcome meta-analyses. These gaps in methodological rigor not only limit the generalizability of our findings

but also underscore the credibility of our evidence. To address these gaps, a core set of outcomes assessment tools specific to indications should be used in prospective clinical research studying cannabinoid use for medical purposes in children. Using a standardized core set of outcomes tools specific to indications in studies exploring the safety and effectiveness of cannabinoids in children would facilitate the accurate capture of effectiveness data, enhancing the quality of evidence and making it future-ready for clinical decision-making. A new core set outcome assessment tool should be developed if an indication-specific core set is unavailable, especially for autism spectrum disorder.

Without standardized tools to assess and grade adverse events to cannabinoids in clinical research, our interpretation of evidence across studies will remain limited due to heterogeneity in reporting. To the best of our knowledge, currently, there is no standardized tool to monitor and grade cannabinoid-related adverse events. There is a need to develop, standardize, and validate cannabinoid-related adverse reporting tool. Standardized cannabinoid-related adverse event monitoring will help to compare adverse events across different studies internationally.

Moreover, we noticed that most of the data on cannabis products used in children for various health conditions were reported retrospectively. This is likely related to the fact that medical cannabis products in Canada do not meet the pharmaceutical standards needed to be evaluated in an interventional study (clinical trial). In a CBD-related spontaneous reports review, quality issues related to unlicensed CBD products used in children for medical purposes were identified. Further literature also highlights concerns with unlicensed CBD products, such as quality, storage, and labeling issues (inaccurate CBD content) and the presence of unintended THC in CBD products. This is a safety concern for pediatric patients accessing medical cannabis, as it is essential to have access to consistent medicines with complete content disclosure.

Currently, cannabis-based products available in the medical cannabis and recreational market do not meet the Good Manufacturing Practices standards that are set out in the Food and Drug Regulations that govern clinical trials in Canada. Product selection in interventional studies remains challenging as international laws decide on cannabis products available for research and purchase in their respective jurisdictions through varying import/export laws hindering multinational trials. Current cannabis-based products vary in cannabinoid composition, CBD THC ratios, and phytocannabinoids, with different products available by different administrative routes for medical use across different jurisdictions. This makes it challenging to generalize our evidence synthesis findings. Jurisdictions across the globe should unite to create international quality standards for medical cannabis products and clinical trials to reduce these barriers to developing a better understanding of the safety and benefits of these products.

4.2 Knowledge mobilization

The current use of cannabinoids for medical purposes among Canadian children is mainly based on anecdotal evidence; disseminating our research findings coast-to-coast will be critical. The Canadian Collaborative for Childhood Cannabinoid Therapeutics (C4T) is a main partner for knowledge mobilization. C4T has a national infrastructure with a multidisciplinary team of more than 130 child health experts, including site leads at each pediatric hospital in Canada, comprising healthcare practitioners, policymakers, parents, and youth partners. Findings from this thesis will be converted into actionable educational insights and shared with a broader range of audiences with the right information and in the right format at the right time to maximize the impact of our research. We will do meaningful youth engagement to design our knowledge translation plan. Key knowledge mobilization strategies to increase the impact of our work include journal publications, C4T newsletters, infographics, lay summaries, open-access online

data portals, poster presentations at scientific conferences, mini podcasts, and short videos/reels on social media platforms.

Findings from each objective have been/will be published in open-access pediatric journals, which are freely accessible to anyone worldwide.(2, 3, 27) In addition to journal articles, concise, evidence-based lay summaries of findings (infographics) have been and will continue to be created to reach a broader audience. Eight posters have been presented at national and international scientific conferences held coast to coast across Canada to fast-track knowledge dissemination, engaging researchers, clinicians, and policymakers. To immediately improve the quality of cannabis-related health research, our search strategies for medical cannabis literature can be accessed freely in an open repository and the supplementary material of published journal articles. R programming scripts used for pharmacovigilance data cleaning are also available on an open science framework.

Infographics for each finding have been/will be prepared and disseminated through C4T after youth partner review, engaging healthcare professionals, clinicians, and parents. Infographics will be uploaded to C4T social media pages, including Twitter (X), Instagram, and TikTok. Additionally, research findings will be shared through educational sessions, and their videos will be recorded and uploaded on YouTube to expand accessibility. Information on cannabinoid-related drug interactions will be shared with the help of podcasts, and they will be shared globally. All data from each section of the thesis will be used to create an online resource portal (publicly available) and inform the design of future innovative clinical trials in children.

4.3 Future research directions

Given the global interest in using cannabinoids for medical purposes in children, international multijurisdictional collaborations are needed to improve the quality of clinical research on cannabinoids and to study their safety and effectiveness in children with precision. There is a need to develop standardized definitions of cannabis products, including the global classification of cannabis products based on CBD and THC ratios and the presence of minor cannabinoids. A core set of outcome assessment tools specific to indications should be used in clinical trials exploring cannabinoid use for medical purposes in children. Cannabinoid-related adverse events were not reported uniformly in the included RCTs in the meta-analysis. A standardized adverse event reporting tool that will enhance adverse event reporting globally is needed, enabling their pooling to develop cannabinoid treatment guidelines for children. We also reported underreporting of data on cannabinoid adverse events in observational and interventional studies in terms of their causality, seriousness, and grading. Measures should be taken to strengthen the reporting of adverse event data in clinical research studies.

A pragmatic approach should be adopted to generate new knowledge on the safety and effectiveness of cannabinoids in the real world with a longer duration of follow-up. Given that in Canada, there is no Drug Identification Number for medical cannabis; there are limited opportunities to study the effects using traditional pharmacoepidemiologic surveillance approaches that rely on administrative health data and drug prescribing codes (drug identification numbers). Pharmacoepidemiological studies such as self-controlled case series and crossover designs studying cannabinoid-related drug interactions in the real world are needed. For these to be successful, trust must be built between the research and patient communities. As cannabinoid responses have been reported to be quite variable, and there is a need for pharmacogenomic

studies to map genetic polymorphisms affecting therapeutic responses and adverse events in children.

Limited evidence informs the safety and benefits of adding minor cannabinoids to cannabis herbal extracts in children. Whole-plant cannabis herbal extracts (including minor cannabinoids) were reported to be beneficial in single-patient case reports only in children with drug-resistant epilepsies and autism spectrum disorder.(28, 29) Cannabidivarin, cannabidiolic acid, and other minor cannabinoids should be studied in children for their long-term benefits and safety, particularly in children with drug-resistant epilepsies and autism spectrum disorder. Various cannabinoids are being used in children with autism spectrum disorder, and there is a need to conduct observational studies informed by family priorities to develop clinical trials to generate safety and benefit data on cannabinoids used in this population. Furthermore, there is limited evidence on the safety and tolerability of cannabis products, excluding those containing THC. THC is the most abundant constituent in the cannabis plant, making it very difficult to remove completely in cannabis herbal extracts. There is a need to explore the risk and benefit profile of adding THC to cannabis herbal extracts used for medical purposes in children. Longitudinal neuroimaging studies that link structural effects with observed clinical effects are needed to understand better the long-term impacts of cannabinoids, including THC and CBD, on the brain, especially in a medical context with repeated exposure over time. Further, the risk of infections and other rare adverse events associated with CBD in real-world settings should be explored.

There is a need to develop therapeutic drug monitoring guidelines for adverse event detection that include plasma levels of CBD and other co-administered drugs for optimal safety monitoring. Most studies that reported on CBD-related drug interactions did not monitor plasma

levels of CBD. To better understand who is at risk for these interactions, more complete data linking relevant clinical outcomes and cannabis-responsive biomarkers is needed.

4.4 Final conclusion

Cannabinoids may be beneficial in children with various indications, but there remains limited evidence of their safety and effectiveness in children for most indications. International collaborations to develop standardized approaches to cannabis research and design prospective clinical research investigating the safety and benefits of cannabinoids in children in the real world are needed. Children receiving cannabinoids, especially CBD, may develop adverse events and should be counseled about potential drug interactions. Similar to starting other medications, physicians considering cannabinoids in children should openly discuss the risks associated with cannabinoids and the lack of long-term safety evidence with parents and caregivers of children. Given the increasing interest in using cannabinoids for medical purposes in children and current knowledge gaps, rigorous studies informed by patients and their families are critically needed to inform clinical care guidelines.

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Chapter 5 Supplementary

5.1 Conference abstracts

1. Manik Chhabra, Mohamed Ben-Eltriki, Arun Paul, Mê-Linh Lê, Lauren E Kelly. (2022). Safety of cannabinoids in children A systematic literature review and meta-analysis. CSPT conference proceedings. Canadian Society of Pharmacology and Therapeutics, Montreal, Canada, https//doi.org/10.1016/j.vascn.2023.107267 Conference date 2022/9.
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