Medical cannabis in children with autism; physician experiences and real-world evidence

by

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A Thesis submitted to the Faculty of Graduate and Postdoctoral Studies of

The University of Manitoba

In partial fulfilment of the requirements of the degree of

Master of Science

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Abstract

Background: Autism can present with a number of neurological and behavioural complexities, and there are no medications approved for symptom management in Canada. Among patients and families, there is growing interest in medical cannabis, particularly for its role in improving behavioural and sleep-related symptoms. However, high-quality evidence regarding its safety, efficacy, and clinical use in children remains scarce, leaving physicians to feel unprepared when faced with parental inquiries.

Methods: This study aims to analyze the current evidence on medical cannabis in children with autism, and to explore the feasibility of future clinical trials in Canada. To achieve this, three complementary approaches are used: (1) a literature review of previously published evidence; (2) a national survey of developmental pediatricians in Canada; and (3) a pharmacovigilance analysis using real-world adverse event reporting databases.

Results: Previously conducted studies of various design types suggest that medical cannabis may improve core and related symptoms of autism in children. However, findings remain heterogeneous and limited by study quality. Survey results showed that developmental pediatricians across Canada were frequently asked about medical cannabis, were concerned about uncertain benefits and safety, coupled with a lack of training and clinical guidance on how to use cannabinoids in children. Most pediatricians expressed willingness to participate in clinical trials that investigated medical cannabis for children with autism. A pharmacovigilance analysis of real-world reporting identified overlapping adverse event patterns across commonly used medication classes but a limited number of cannabinoid-related reports in children with autism. Reports of adverse events to cannabinoids in children with epilepsy, where cannabidiol is on label, were identified which suggests the limited reports in children with autism may be underreported as all medical cannabis use being off-label in children with autism.

Conclusions: The results of these studies indicate that there is insufficient evidence to support the clinical use of cannabinoids in the management of children with autism. Real-world data implications are limited due to under-reporting and a lack of Canadian data. Growing clinical interest alongside these knowledge gaps highlight the urgent need to conduct well-structed pediatric cannabinoid clinical trials in Canada and emphasize the need for enhanced physician education with harmonized systems for rigorous safety monitoring.

Acknowledgements

I would like to sincerely thank my supervisor, Dr. Lauren E. Kelly, for all of her guidance throughout my graduate studies. Your support, patience, and encouragement over the past two years have been incredibly important to me. Through our meetings and discussions, I gradually developed a clear understanding of both the scientific and clinical significance of this research. Thank you for continuously encouraging me to think and improve my work. I believe that I am growing as a researcher during this period.

I would also like to thank my committee members, Dr. Henry Dunn and Dr. Geert W. ’t Jong, for their thoughtful feedback and valuable suggestions. Each committee meeting shared with me their knowledge and experience. These helped strengthen my research and broaden my understanding of this field. I am also grateful to Dr. Sachin Katyal for serving as chair of my examining committee and for his support during the defense process.

I would also like to thank everyone who contributed to this work, including caregivers, developmental pediatricians, and specialists; without them, I could not have completed this perfect questionnaire. Additionally, I want to especially thank all the lab members. From the moment I joined the lab, I have received invaluable assistance every time I encountered a problem, enabling me to successfully complete each task.

I have been fortunate to work within a supportive research environment throughout my graduate training. Thank you to everyone for your discussions, encouragement and experience sharing, which made my graduate journey even more meaningful.

Finally, I would like to thank my family and friends for their constant support. Their support and understanding helped me through the challenges of graduate studies and gave me the confidence to continue moving forward.

Contributions of Authors

Chapter 3 is based on the manuscript entitled “Perspectives from developmental pediatricians on medical cannabis in children with autism.” The contributions of the authors to this work are described below.

Author	Contribution
Wanting Ding	Study development, survey administration, data collection, data analysis and interpretation, literature review, and preparation of the original manuscript draft.
Lauren E. Kelly	Study conception and design, supervision, funding acquisition, interpretation of findings, and critical review and revision of the manuscript.
Holly Mansell	Methodological input, survey development, and critical review of the manuscript.
Jessica Overby	Survey development, methodological input, interpretation of findings, and critical review of the manuscript.
M. Florencia Ricci	Clinical and methodological input, survey development, and critical review of the manuscript.
Naomi Goloff	Clinical input, survey development, and critical review of the manuscript.
Sara Klassen	Survey development

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Chapter 1: Introduction and Background

1.1 Autism

Autism is a complex neurodevelopmental disorder characterized by persistent impairments in social communication and interaction, as well as restricted and repetitive patterns of behavior.[1] The presentation and severity of these symptoms vary from individual to individual, ranging from mild functional impairment to severe impairment requiring lifelong support.[2] Autism is typically diagnosed in early childhood, with core symptoms usually emerging between 12 and 24 months.[3] Diagnosis is based on clinical criteria outlined in diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and is often complicated by co-occurring developmental or psychiatric disorders.[4,5]

Over the past several decades, reported rates of autism have increased significantly. According to the latest estimates from Health Canada in 2018, approximately 1 in 50 children under the age of 18 has been diagnosed with autism.[6] This increase may reflect increased awareness of screening, diagnosis and broadening of diagnostic criteria, but a real increase in prevalence cannot be ruled out.[7] Therefore, it raises growing demand for timely diagnostic, educational, and clinical services. Many provinces face long wait times for both initial consultations and formal diagnostic assessments, leaving families in uncertainty during a critical period of their children's development.[8,9] Educational systems often lack the capacity to adequately support children with special needs, and children with autism in particular face significant challenges in learning and integrating into the classroom environment.[10,11]

The high comorbidity rate is one of the major challenges in managing autism.[12] Recent systematic reviews have confirmed that a majority of children with autism experience one or more comorbid conditions, with prevalence estimates ranging from 70% to 90%, depending on type of comorbidity.[13] These conditions include attention deficit hyperactivity disorder (ADHD), anxiety disorders, depression, sleep disorders, gastrointestinal (GI) problems, and epilepsy.[13,14] One study reported a 36.84% prevalence of at least one psychiatric comorbidity in children with autism.[15] Psychiatric comorbidities may mask or mimic core autism symptoms, further complicating diagnosis and treatment planning.[16] The cumulative burden of comorbidities can lead to greater functional impairment and therefore requires more careful management.[17] In many cases, this population are prescribed multiple medications to treat different symptoms, increasing the risk of drug interactions and adverse reactions.[17] Caregivers often must navigate these complex treatment decisions while also coping with chronic stress, fatigue, and uncertainty, especially when faced with multiple options.[18] These factors focus on the importance of comprehensive, personalized care that addresses not only behavioural symptoms but also broader developmental, medical, and social challenges.

Despite extensive research, the causes of autism remain unclear. Genetic, environmental, and

prenatal risk factors have been implicated, but to date, no definitive cause or prevention strategy has been identified. [19,20] Due to this, families lack evidence-based prevention options, and clinical care is limited to symptom management. [21]

Together these, there is an urgent need to explore more effective, affordable and accessible treatment options.

1.2 Current Management Approaches for Autism

The symptoms and severity of autism vary widely, and its management requires a highly individualized and multidisciplinary approach. Although there is currently no single, universally effective approach to improvement, a combination of behavioural, educational, and pharmacological strategies is often used to manage symptoms, improve functioning, and enhance quality of life.[22] However, these approaches often have limitations in accessibility, effectiveness, or tolerability, prompting many families to seek alternatives when conventional approaches are insufficient.[23]

Currently, approaches to managing symptoms of autism rely primarily on behavioural interventions, particularly for young children, such as applied behavior analysis (ABA), which is the most widely used and researched approach.[24,25] Some children benefit from these programs, but they require significant time, financial resources, and long-term family commitment, making them inaccessible or difficult for many children to sustain.[26] Furthermore, concerns have been raised about the universal applicability of these approaches, as individual responses vary widely, and many children make only modest or inconsistent progress.[27]

Medications may be used alongside behavioural and educational interventions to manage concurrent psychiatric or behavioural symptoms, including irritability, aggression, hyperactivity, anxiety, depression, sleep difficulties, and self-injurious behaviors.[28] However, currently available medications primarily target these associated symptoms rather than the core symptoms of autism. Many surveys show that the core symptoms that parents most want to improve for their children with autism are disorders of social communication and social interaction.[29]

Several classes of medications are used for symptom management in children with autism. The atypical antipsychotics, such as risperidone and aripiprazole, are commonly prescribed and the only medications approved by the U.S. Food and Drug Administration (FDA) to treat irritability associated with autism in children. However, a significant number of children experience adverse effects such as sedation, weight gain, and metabolic disturbances.[26,28,30] Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or sertraline can help manage anxiety and depression, stimulant medications such as Methylphenidate (Ritalin) can help address hyperactivity and inattention, and melatonin can be used to treat sleep disturbances.[17,31,32] However, many of these medications are used off-label in children with autism, and evidence supporting their efficacy is limited.[33] Evidence of efficacy varies according to the medication and the symptom being targeted. Research suggests that many parents explore

complementary Alternative Medicine, such as dietary interventions and acupuncture, due in part to concerns about adverse effects of conventional medications. Clinicians are often open to these approaches, provided they are used safely and in conjunction with standard care.[34]

Polypharmacy is another common concern.[35] In many cases, children with autism are prescribed multiple psychotropic medications to address different symptoms. This may increase the risk of drug-drug interactions and adverse effects and may complicate long-term clinical management.[35] A recent clinical guideline emphasizes that treatment strategies for co-occurring symptoms in affected children should differ from those used in neurotypical populations, recommending tailored approaches to reduce unnecessary polypharmacy and promote safer alternatives.[17]

Given the multiple challenges presented by autism, including its complex presentation, high comorbidity burden, lack of understanding prevention strategies, and limitations of behavioural and pharmacological interventions, families and clinicians are increasingly exploring alternative treatment options. The pharmacological agents most frequently used in children with autism, together with their associated adverse effects, are summarized in Table 1. The limitations and adverse effects of existing pharmacological options contribute to family interest in alternative approaches, including medical cannabis. [36]

Table 1. Cannabinoids and commonly used medications in autism and their reported symptoms and safety profile (common adverse effects)

Drug class	Representative Agents	Target symptoms	Common Adverse Effects
Atypical antipsychotics	Risperidone, Aripiprazole	Irritability, aggression	Sedation, weight gain, metabolic disturbances, akathisia
Antidepression	Fluoxetine, Sertraline	Anxiety, depression	GI upset, insomnia, behavioural activation
Stimulants	Methylphenidate	Hyperactivity, inattention	Appetite suppression, irritability, insomnia
Melatonin	Melatonin	Sleep problems	Daytime sleepiness, dizziness
Medical Cannabis	CBD-rich/CBD-predominant oils/oral drops	Irritability, aggression, anxiety, sleep problems	somnolence, drowsiness, appetite changes, GI problems

1.3 Medical Cannabis

Cannabis is one of the oldest plants cultivated and used by humans, with a medicinal history dating back thousands of years; it was commonly used in ancient civilizations for pain relief, sedation, anti-inflammation, and sleep induction.[37] Medical cannabis refers to the use of cannabis and its derivatives for therapeutic purposes under medical supervision and regulatory

frameworks.[38] Cannabis has long been controversial due to its psychoactive effects and potential for abuse. Only in recent decades has it transitioned from being considered primarily a controlled substance to being reexamined in medical research.[38,39] Its reintroduction into modern medicine is driven by patient advocacy, evolving legal and regulatory environments, and growing evidence of the potential therapeutic benefits of cannabinoids for selected medical conditions.[39] Nonetheless, concerns about its safety persist, including reports of serious adverse reactions and increased risks of short-term adverse events.[39]

Therefore, an increasing number of countries have established comprehensive regulatory frameworks to govern the medical use of cannabis.[40] In Canada, medical cannabis was legalized in 2001, and its scope was further expanded by the Cannabis Act 2018, providing access to patients with various conditions.[41] Currently, Canada allows physicians to prescribe cannabis for patients with specific medical indications, and licensed producers supply the products.[41] For example, medical cannabis has shown therapeutic potential across several areas, including seizure control, pain management, and relief of chemotherapy-induced or palliative symptoms.[42] The strength of evidence for these indications varies. Clinical trial data is relatively robust for epilepsy and chronic pain, while other indications rely more on observational studies or patient self-reported outcomes.[43,44] Despite differences in evidence strength, the demand for medical cannabis has increased significantly, reflecting unmet clinical needs and patients' preference for alternative or complementary therapies.[45]

Public interest in cannabis therapies has also extended to vulnerable populations, including children and individuals with neurodevelopmental disorders.[46] Parents and caregivers are increasingly inclined to use cannabis-derived products as adjunctive or supportive therapies, concerned about the side effects of conventional medications and viewing cannabis as a more "natural" alternative.[47] This trend raises clinical concerns and ethical debates, highlighting the need for rigorous research to determine the safety and efficacy of medical cannabis in vulnerable populations and to develop appropriate guidelines for its use.[48]

1.4 Pharmacology of Medical Cannabis

The pharmacological effects of cannabis are primarily mediated through interactions with the endogenous cannabinoid system (ECS).[49] The ECS is a complex regulatory network responsible for maintaining physiological homeostasis and playing a crucial role in regulating numerous cognitive and physiological processes.[49] It is composed of cannabinoid receptors, endogenous ligands, and metabolic enzymes.[49] The two best-characterized receptors, cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), differ in their distribution and functions.[49] CB1 receptors are primarily distributed in the central nervous system, particularly in brain regions associated with cognition, memory, and motor control, where they exert their effects by regulating neurotransmitter release. CB2 receptors are primarily distributed in the immune system and peripheral tissues, participating in the regulation of inflammation and immune

responses and can be upregulated in the central nervous system under pathological conditions.[49,50] In addition to CB1 and CB2, other receptors and ion channels (such as transient receptor potential vanilloid 1 (TRPV1), peroxisome proliferator-activated receptor alpha (PPAR-α), and G protein-coupled receptor 55 (GPR55)) also mediate some of the effects of endocannabinoids, particularly anandamide (AEA).[51] Major endogenous ligands include AEA and 2-arachidonoylglycerol (2-AG), which are natural agonists of CB1 and CB2 receptors.[49]

Among the phytocannabinoids found in Cannabis sativa, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most extensively studied.[52] THC is a partial agonist at both CB1 and CB2 receptors, exhibiting psychoactive properties and analgesic properties for chronic and neuropathic pain. It also stimulates appetite in cancer patients, reduces nausea and vomiting in chemotherapy patients and improves sleep quality.[53–55]

CBD, in contrast, has little direct affinity for CB1 or CB2 receptors but exerts effects through multiple molecular pathways.[56] CBD has been proposed to influence endocannabinoid signalling indirectly, including through inhibiting fatty acid amide hydrolase (FAAH) and reducing AEA metabolic, although these mechanisms remain uncertain.[56] CBD also interacts with several non-cannabinoid targets, including TRPV1, GPR55, serotonin 1A (5-hydroxytryptamine 1A; 5-HT1A) receptors, and PPARγ.[56] Through these diverse actions, CBD demonstrates anticonvulsant, anxiolytic, antipsychotic, neuroprotective, and anti-inflammatory properties, without producing intoxication.[57] This poly-pharmacology shows its therapeutic promise across neurological and immune-related disorders.[57]

Both THC and CBD are extensively metabolized in the liver, and their degradation is crucial for understanding safety issues and potential drug interactions.[58] Cytochrome P450 (CYP) enzymes are a major family of hepatic enzymes which is working for metabolism of many medications. THC is primarily metabolized by CYP2C9, CYP2C19 and CYP3A4, while CBD is primarily metabolized by CYP2C19 and CYP3A4.[58] Variation in these enzymes, whether due to genetic polymorphisms or concomitant medication use, can significantly affect plasma cannabinoids levels, thereby increasing the risk of adverse reactions.[59] In addition to serving as substrates, cannabinoids may act as inhibitors of various metabolic enzymes.[60,61] CBD inhibits multiple CYP enzymes, and both THC and CBD have been shown to inhibit uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes, particularly UGT1A9 and UGT2B7, which are involved in the glucuronidation and clearance of many medications. [60] Inhibition of these pathways potential slows the clearance and increases the exposure of medications commonly prescribed in children with autism, led to increasing the potential for clinically relevant drug-drug interaction.[62,63] However, the clinical significance depend on the dosage, formulation, duration of exposure, and concomitant medications of the cannabinoid; therefore, potential interactions should be evaluated on a drug-specific basis.

Pharmacokinetics of medical cannabis are complex influenced by route of administration, formulation, and patient-specific factors.[69] Oral preparations are subject to significant first-pass metabolism, resulting in variable bioavailability and delayed onset, whereas inhaled routes provide rapid systemic absorption but shorter duration of action.[68,69] Furthermore, pharmacokinetic differences during childhood development must be considered.[64] Age-related variations in volume of distribution, oral bioavailability, and clearance can significantly influence cannabinoid exposure in children of different ages.[64,65] However, these developmental differences remain poorly characterized, and pediatric cannabinoid pharmacokinetics remains an underdeveloped area of research. Therefore, these pharmacokinetic differences contribute to variability in cannabinoids exposure and complicate the development of dosing strategies, especially in pediatric population, highlighting the importance of careful dose adjustment and close monitoring when cannabinoids are used in combination with other therapies.

In this context, the motivations and patterns of medical cannabis use in clinical practice are particularly concerning. Many patients report using medical cannabis as an adjunct to existing psychotropic or antiepileptic medications, making careful assessment of concomitant medication use.[65,66] At the same time, unsupervised or excessive use is risky. Heavy or chronic exposure, particularly when initiated at a young age, is associated with neurocognitive effects, psychiatric symptoms, and the development of cannabis use disorder.[67] These findings underscore the importance of careful titration, dosing, and monitoring to balance therapeutic benefits with known risks.

Beyond THC and CBD, other phytocannabinoids such as cannabigerol (CBG), cannabinol (CBN), nabilone, dronabinol, dexanabinol, levonantradol, tetrahydrocannabinolic acid (THCA), cannabidiolic acid, and cannabidivarin, together with terpenes, may contribute to therapeutic outcomes through the so-called “entourage effect.”[68] This concept proposes that interactions among cannabinoids and other plant constituents may influence clinical effects; however, convincing clinical evidence for predictable therapeutic synergy remains limited.[68,69] Ongoing research is therefore essential to clarify optimal formulations and administration strategies that maximize benefits while minimizing risks.

1.5 Medical Cannabis in Autism

All medical cannabis (use of cannabinoid- containing products) used for the management of autism or its associated symptoms are currently used off-label, as no cannabinoid product has been approved specifically for autism.[70] Epidiolex, a purified prescription formulation of cannabidiol (CBD), is currently the only approved medical cannabinoids product by the U.S. Food and Drug Administration for the treatment of seizures associated with Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis.[71] Against this backdrop, medical cannabis has gradually gained public and academic attention.[42] In addition to irritability, anxiety, sleep disturbances, hyperactivity, and aggressive behavior, core social communication impairments

and stereotyped behaviors are also of primary concern to parents of children with autism, who hope their children will gradually achieve greater independence.[13,14,26] Traditional drug treatments, however, primarily target accompanying symptoms, are largely ineffective against core features, and are often associated with significant adverse effects.[28] It is hoped that it can alleviate some common symptoms while reducing the adverse effects associated with traditional medications and exploring potential areas where current therapies have not adequately addressed, making it a novel yet controversial research direction.

The rationale for considering medical cannabis in autism lies in the overlap between autism pathophysiology and processes regulated by the endocannabinoid system (ECS).[71] Research indicates that an imbalance in excitatory and inhibitory (E/I) signaling, particularly disturbances in glutamate and gamma-aminobutyric acid (GABA) pathways, is believed to be a key driver of neural network hyperexcitability and behavioural abnormalities.[72] Similarly, neuroinflammation and microglial activation are frequently observed in the brain tissue and immune profiles of individuals with autism, and the immune-regulatory functions of the ECS and the anti-inflammatory effects of CBD may play a role.[71] Furthermore, the heightened stress and anxiety responses often exhibited by individuals with autism are closely linked to the ECS's regulation of mood and stress pathways.[73] Overall, these overlapping mechanisms provide biological plausibility for exploring the use of cannabinoids in the management of autism, but current evidence remains primarily theoretical and in early clinical observations.

Emerging clinical evidence provides cautious support but remains inconclusive. Several prospective observational studies and caregiver surveys (primarily from Israel, Canada, and the United States) have demonstrated improvements in irritability, aggression, anxiety, and sleep problems in children after using CBD-enriched preparations, with some parents also reporting reduced self-injurious behaviors and improved daily functioning.[74] Nevertheless, these results largely rely on subjective caregiver assessments, lack placebo control, and vary widely in dosing regimens. Randomized controlled trials are limited in number. One study in children with autism showed some efficacy in improving disruptive behavior with a CBD-rich cannabis extract, but the primary endpoint did not reach statistical significance, and the placebo effect was significant.[74] This difference may reflect expectancy effects, caregiver-reported outcomes, flexible dosing, or the concurrent modification of other medications. A small number of exploratory studies of cannabidiol (CBD) or cannabidivarin (CBDV) suggest that they may modulate cortical excitability markers and lead to improvements in irritability, aggression, anxiety, and social functioning , but the evidence remains preliminary.[74]

Safety data from pediatric autism cohorts have been mixed. The most common adverse events include drowsiness, altered appetite, gastrointestinal disturbances, and irritability, with most events considered mild to moderate.[75] Tetrahydrocannabinol (THC) poses the greatest concern due to its psychoactive properties, potential cognitive effects, and long-term risks for neurodevelopment.[53] Although CBD-based formulations are more commonly investigated in

pediatric populations, potential interactions with anti-epileptic medications and elevated liver enzymes have been observed.[76] Of note, most existing studies have been of short duration, so long-term safety and efficacy remain unclear.[65]

Overall, while most existing studies of medical cannabis in autism have focused on managing associated challenges such as irritability, aggression, anxiety, and sleep disturbances, emerging evidence also suggests potential benefits for certain core features of autism, including social communication and repetitive behaviors.[74,77] Nevertheless, these findings remain preliminary, inconsistent, and often come from small or uncontrolled studies. The current body of evidence highlights both the promise and the considerable uncertainty surrounding cannabinoids in autism, underscoring the need for rigorous trials that address safety, long-term outcomes, and ethical considerations before such therapies can be responsibly integrated into clinical care.[78]

1.6 Barriers and Ethical Considerations

The evaluation of medical cannabis in autism is complicated by a number of interrelated barriers.[21] Historically, cannabis has been widely available for recreational use, yet its medical applications have often been introduced without the same level of regulatory oversight applied to conventional pharmaceuticals.[37,70] This inconsistency has created challenges for data collection and pharmacovigilance, since product labeling, cannabinoid concentrations, and patterns of use are highly variable.[69,74] Reliable epidemiological data are limited. This results in no ability to generate a clear safety profile or establish standardized dosing recommendations.[79]

The clinical evidence to date has important methodological limitations. Many studies include small samples and short follow-up periods.[83] Observational or uncontrolled designs are common, with preliminary reports indicating improvements in irritability, anxiety, sleep, and even select core symptoms.[28,74] Some studies have also described reduced use of concomitant medications, reduced parental stress, and fewer seizures among children with co-occurring epilepsy.[74,84] However, these findings have not been consistently replicated in adequately randomized trials due to the lack of standardized outcome measurement tools.[62] Reported differences may also reflect expectancy effects, concurrent interventions, or modifications to other medications. Ongoing phase III clinical trials are currently evaluating a CBD product for autism in Australia, and early safety phases have been completed but are not published yet.

Adverse reactions represent another key limitation of the current evidence. Common reported adverse events include drowsiness, changes in appetite and weight, irritability, and, in rare cases, psychosis.[74,84] Potential drug interactions are also clinically relevant, particularly when cannabis products are used with antipsychotics and antiepileptic medications. These combinations may increase sedation or alter medication exposure through shared metabolic pathways. However, the availability of long-term safety information still limited and neurodevelopmental effects remains insufficiently characterized.

Cannabis use disorder and dependence represent separate concerns, particularly with repeated exposure to THC-containing products during adolescence.[85] Although most medical protocols emphasize CBD-dominant formulations, many preparations still use mixtures and some are unregulated. These risks complicate long-term follow-up, as study dropouts or inconsistent adherence often led to missing data, obscuring the understanding of sustained benefits or harms.[36,74,86] As a result, it remains uncertain whether early improvements are sustained or whether uncommon harms emerge over time.

Social and cultural factors also affect the generalizability of the evidence generated and clinical communication due to hesitancies to report or ask about cannabis. Cannabis continues to carry significant stigma, particularly in relation to children which may limit reporting.[80] This may lead to underreporting of use by families and reluctance among clinicians to engage in open discussions.[80,81] This sociocultural and professional hesitation, along with a lack of standard tools or education reduce opportunities to systematically collect data and leaves both families and health care professionals with limited guidance.[82] At the same time, regulatory complexity can make trials difficult to conduct. Existing perceptions about cannabinoids and uncertainty about long-term effects may influence family participation in clinical trials. Most available evidence comes from small observational cohorts or caregiver reports which are not powered to answer questions about efficacy limit abilies.[83]

Ethical concerns compound these scientific limitations. Children with autism are a vulnerable group, raising challenges in assent and informed consent when the long-term neurodevelopmental consequences remain unknown.[87–91] Researchers also note that the lack of clarity regarding the long-term risks of medicinal cannabis use makes recruitment and retention of participants difficult, further challenging the expansion of research data.[36,86] Furthermore, inequities in access, driven by socioeconomic status, geography, and evolving legal frameworks, raise questions of fairness in who benefits from these therapies.[9,10]

In conclusion, the current evidence does not support the routine use of cannabinoids to manage autism or its associated symptoms. Therefore, before medical cannabis can be responsibly integrated into pediatric care, rigorous, ethical trials, standardized outcome measures, and long-term monitoring are urgently needed to establish its efficacy and safety.

1.7 Knowledge Gaps and Rationale for This Study

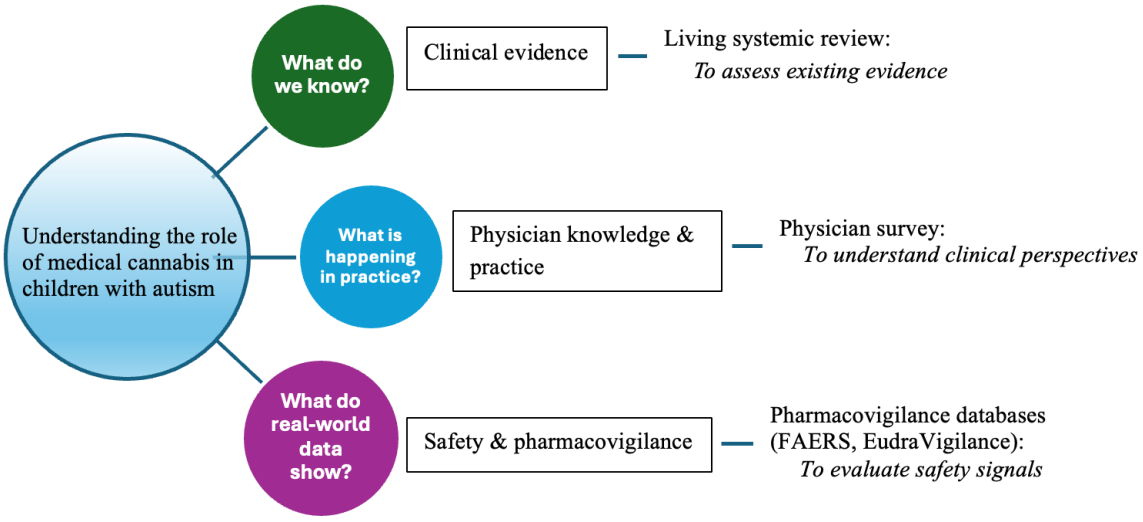
Although there is growing interest in the therapeutic potential of cannabinoids for children with autism, knowledge in key areas remains underdeveloped. Available information is scattered across small-scale studies and case reports, with few synthesizing findings into a coherent body of evidence. [70,78,92] Consequently, clinicians and families lack clear guidance on potential therapeutic benefits, safety considerations, and appropriate use.[28,65]

In parallel with this limited evidence base, there is a striking lack of clarity around how physicians are currently responding to the increasing number of inquiries from families.[45,82] Medical cannabis is often raised as an option when traditional interventions fail to achieve meaningful improvements, yet many pediatricians report feeling underprepared to provide guidance.[93–96] The absence of standardized training, clinical guidelines, and institutional support has created a situation in which families may not receive balanced information from trusted providers.[97] In some cases, they turn instead to online communities or non-medical sources of advice, reinforcing stigma and limiting opportunities for safe monitoring.[98–100] Understanding the perspectives, experiences, and challenges faced by pediatricians is therefore critical to bridging the gap between emerging research and everyday practice.

Equally important is the lack of robust safety data derived from real-world contexts. Children with autism frequently require multiple medications, including antipsychotics, antidepressants, and antiepileptics, which raises the possibility of drug-cannabinoid interactions and cumulative risks.[101,102] Nevertheless, existing literature rarely systematically addresses these issues. Traditional clinical trials are not designed to capture rare or unexpected events, nor do they reflect the full complexity of polypharmacy that characterizes this population.[103,104] Large pharmacovigilance databases, which collect spontaneous reports of adverse events, are used primarily to characterize the background adverse-event environment associated with medications commonly used in children with autism.[105–107] Integrating such data with clinical and research perspectives offers a more complete picture of safety in practice.

These persistent gaps, in the synthesis of published evidence, in the understanding of physician experience, and in the systematic monitoring of real-world safety, provide the rationale for the present study. As shown in Figure 1, this study employs three complementary strategies: a literature review, a nationwide physician survey, and an analysis of pharmacovigilance databases. By triangulating findings across these approaches, the study aims to generate a more comprehensive and clinically meaningful understanding of cannabinoid use in children with autism spectrum disorder, including therapeutic potential, safety considerations, and persisting gaps in knowledge. In doing so, it aims to lay the foundation for future clinical trials and evidence-based guidance, supporting Canadian families and clinicians in making informed, safe, and ethical decisions regarding medical cannabis use.

Figure 1. Schematic of knowledge gaps in medical cannabis use for autism and the approaches in this thesis designed to address them.



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Chapter 2: Cannabinoids for Symptom Management in Children with Autism: Evidence from Published Clinical Studies

2.1 Abstract

Background: Autism is a complex neurodevelopmental disorder, often accompanied by behavioural challenges, anxiety, sleep disturbances, and other comorbid symptoms. Current drug strategies have limited effectiveness and may cause adverse reactions. Cannabinoids have emerged as a potential alternative therapy for symptom management; however, their efficacy and safety in children with autism remain unclear.

Methods: Studies involving children with autism were identified through a broader ongoing living systematic review of cannabinoid-based products in children and were analyzed as a systematic review for present study. Systematic database searches and independent screening by two reviewers were conducted using Covidence. Data on study design, population, interventions, efficacy outcomes, and adverse events were extracted and synthesized. A subgroup analysis on randomized controlled trials was conducted.

Results: A total of 41 studies involving 4,179 participants were included. This consists of 5 randomized controlled trials, 7 single-arm trials, 9 observational studies, 6 cross-sectional surveys, 2 chart reviews, 3 case series, and 7 case reports. Observational studies frequently reported improvements in irritability, anxiety, sleep, communication, social functioning, and quality of life. However, results from randomized controlled trials were inconsistent. Although all trials have reported improvements in secondary outcome measures, including social functioning, anxiety, and caregiver stress, the primary outcome measure is usually not significantly different from the placebo group. Adverse events are primarily mild to moderate. Common side effects reported included drowsiness, gastrointestinal symptoms, and appetite changes. Rare neuropsychiatric adverse events, including psychosis, were also reported.

Conclusion: Cannabinoids may offer potential benefits for symptom management in children with autism, but current evidence is limited and heterogeneous. Heterogeneous study design, small sample sizes, lack of control groups, and inconsistent outcome measures limit confidence in recommendations. High-quality randomized controlled trials with standardized outcome measures and long-term safety data are needed to inform clinical practice.

2.2 Introduction

Autism is a complex neurodevelopmental disorder characterized by differences in social communication, restricted interests, and repetitive behaviors.[1] Many children with autism experience a wide range of co-occurring conditions, contributing to substantial variability in

symptom presentation and treatment response.[2–6] Current pharmacological approaches primarily target associated symptoms, with commonly used medications.[7–9] However, these therapies are often associated with modest benefits and may result in significant adverse effects such as sedation, weight gain, metabolic disturbances, and behavioural changes.[10,11] In addition, many children with autism are exposed to polypharmacy, increasing the risk of drug-drug interactions and cumulative adverse effects.[12,13] These limitations highlight an unmet need for alternative or adjunctive therapies that are both effective and well tolerated.

Cannabinoids, including cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), have emerged as potential options for managing autism-related symptoms.[14,15] These compounds act on the endocannabinoid system, which is involved in neurodevelopment, synaptic plasticity, and regulation of mood and behavior.[16,17] Preclinical and early clinical studies suggest that modulation of this system may influence both core and associated symptoms of autism.[18–20] In particular, CBD has been associated with potential anxiolytic, antipsychotic, and anti-inflammatory effects, while THC may contribute to symptom modulation through central nervous system activity.[21–24] Preliminary clinical evidence has reported improvements in irritability, anxiety, sleep, and quality of life in some patients receiving cannabinoid-based treatments.[25–29]

Despite growing interest, the current evidence base remains limited and methodologically challenging.[30] Studies vary widely in cannabinoid formulations, CBD-to-THC ratios, dosing regimens, routes of administration, and duration of treatment.[31] Individual variability in response is substantial, reflecting differences in age, comorbidities, concomitant medications, and underlying neurobiology.[32–34] In addition, many studies rely on caregiver-reported outcomes, small sample sizes, or uncontrolled designs, increasing the risk of bias and limiting the generalizability of findings.[1,35–37] Standardization of dosing remains particularly challenging, as optimal therapeutic ranges for cannabinoids in pediatric populations are not well established.[38]

In parallel with these scientific uncertainties, real-world interest in cannabinoid use for children with autism has increased substantially.[39] Caregivers frequently seek alternative approaches when conventional methods are insufficient or poorly tolerated, often targeting symptoms such as anxiety, aggression, and sleep disturbances.[40] In Canada, the legalization and increasing accessibility of cannabis products have further contributed to this growing demand.[41] However, this rise in use has not been matched by high-quality clinical evidence or clear clinical guidelines, leaving clinicians with limited evidence to guide decision-making.[42,43] This mismatch between clinical demand and available evidence underscores the importance of systematically evaluating current data to inform both clinical practice and future research.[34,44]

Given these uncertainties, a comprehensive synthesis of the available evidence is needed to better understand the potential benefits and risks of cannabinoid use in children with autism.

Therefore, this systematic review aims to summarize current evidence on the efficacy and safety of cannabinoids in this population and to evaluate the strength and limitations of the existing literature. To explain the heterogeneity in study design, findings from randomized controlled trials were also analyzed separately.

2.3 Methods

This autism-specific systematic review was embedded within a broader living systematic review of pediatric medical cannabis use registered with the Open Science Framework (OSF).[45,46] The review was conducted in accordance with Cochrane systematic review methodology and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and PRISMA-S guidelines.[47,48]

Eligibility criteria

The research question for this review was: *"What evidence is available regarding the efficacy and safety of cannabinoid-based products used for symptom management in children with autism?"*

We included studies involving children and adolescents aged 18 years or younger with autism who received cannabinoid-based products for the management of autism-related symptoms or associated comorbidities. Studies of all designs were considered, including randomized controlled trials (RCTs), non-randomized controlled trials, single-arm open-label studies, prospective and retrospective observational studies, cohort studies, case-control studies, cross-sectional surveys, qualitative interviews, chart reviews, case series, and case reports. Conference abstracts were also included when sufficient outcome data were available.

Eligible interventions included both pharmaceutical cannabinoids and plant-derived cannabinoid products, whether prescribed medically or self-administered by caregivers. Cannabinoids of interest included cannabidiol (CBD), delta-9-tetrahydrocannabinol (THC), CBD- or THC-dominant cannabis extracts, nabilone, dronabinol, dexanabinol, levonantradol, tetrahydrocannabinolic acid (THCA), cannabidiolic acid, and cannabidivarin. Studies reporting any efficacy or safety outcomes related to cannabinoid use were eligible for inclusion. Outcomes of interest included cannabinoid formulation, dosing, route of administration, treatment duration, symptoms targeted, efficacy outcomes, adverse events, serious adverse events, and treatment discontinuation. Studies involving recreational cannabis use, accidental cannabinoid exposure, editorials, narrative reviews, expert perspectives, and letters to the editor were excluded.

Search strategy

Studies for this systematic review were extracted froman updated search conducted as part of the broader living systematic review of pediatric medical cannabis use (CRD42020187433)

completed by a health sciences librarian (ML). The original search strategy was expanded through the addition of autism-related search concepts. Searches were conducted by experienced health sciences librarians using MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), PsycINFO (EBSCO), Cochrane Library, Web of Science Core Collection, and Google Scholar. Grey literature sources included the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov, Scopus conference abstracts, PapersFirst (OCLC), ProceedingsFirst (OCLC), ProQuest Dissertations & Theses Global, and the Networked Digital Library of Theses and Dissertations. No language restrictions were applied. Forward and backward citation chaining of included studies was conducted using Scopus. References from relevant systematic and scoping reviews were also screened.

Study selection and data extraction

Title and abstract screening, full-text review, data extraction, and quality assessment were independently performed in duplicate by two reviewers. Disagreements were resolved through consensus or consultation with a third reviewer. Extracted study characteristics included study design, country, study setting, participant demographics, autism diagnostic criteria, sample size, cannabinoid formulation, dose, route of administration, treatment duration, comorbidities, concomitant medications, and reported efficacy and safety outcomes. Due to substantial heterogeneity in efficacy outcome measures across studies, all reported efficacy outcomes were descriptively synthesized. Particular attention was given to outcomes related to irritability anxiety, sleep, communication, social interaction, repetitive behaviors, caregiver stress, and quality of life. Safety outcomes included adverse events, serious adverse events, treatment discontinuation, withdrawal due to adverse events, and specific reported adverse reactions. Methodological quality assessments for non-randomized studies previously included in the original living systematic review were retained from the original review. Risk of bias and methodological quality were assessed using the Cochrane Risk of Bias tool for randomized controlled trials and finished by two reviewer.[49]

Data synthesis

Due to significant heterogeneity in study design, cannabinoid formulations, dosing strategies, participant characteristics, and reported outcome measures, only descriptive summaries were performed on the efficacy and safety results of the included studies. Efficacy outcomes were grouped into clinically relevant domains, including behavioural symptoms, anxiety, sleep problems, cognition, communication, caregiver stress, quality of life, and associated comorbidities. Randomized controlled trials were examined separately to better assess whether efficacy findings observed in observational studies were supported by higher-quality evidence. Safety findings were categorized according to adverse event type, including commonly reported adverse events, serious adverse events, and reported neuropsychiatric effects.

2.4 Results

The study selection process is summarized in Figure 1. A total of 41 studies were included in this systematic review, representing 4,179 participants across a wide range of study designs.

The included evidence base was highly heterogeneous, comprising randomized controlled trials (n = 5)[25–29], single-arm interventional studies (n = 7)[50–56], observational studies (n = 9)[3,35,57–63], cross-sectional surveys (n = 6) [36,64–68], qualitative interviews (n = 2)[69,70], chart reviews (n = 2)[71,72], case series (n = 3)[73–75], and individual case reports (n = 7) [4,37,76–80] (table 1). Controlled trials were relatively few, while descriptive or exploratory studies were more prevalent.

The characteristics of the included studies varied by geographic location, study design, and population. Most studies were conducted in North America[27,4,36,36,37,52,54,63–68,70,72,73,77], South America[3,29,61,62,71,74,78,79], and Israel[25,50,51,57–59], with a smaller number in Europe[35,60,80] and Australia[26,28,53,55,56,75,76]. It shows a global but regionally diverse distribution of evidence. Study sizes ranged from case reports to large surveys involving over 1000 participants[67]. Most studies were single center, with only a few multi-center studies[55,58,65]. Study durations varied widely, ranging from short-term intervention trials of about one month to observational follow-ups of up to two years. Most intervention studies had relatively short durations, while observational studies tended to have longer follow-up periods. [35,37,63,67]

Among the included studies, most participants were children with autism; however, a few case reports and case series included adults who had started using cannabis in childhood.[73,78] Reporting of demographic characteristics was inconsistent, and some studies lacked detailed information on sex distribution and baseline characteristics, making direct comparisons of outcomes difficult.

Case report and case series studies typically lack comprehensive reporting of patient demographics and post-intervention outcomes, limiting their interpretability and general applicability. Observational studies also exhibit inconsistencies between baseline characteristics and follow-up data reporting. Cross-sectional surveys are typically limited by incomplete descriptions of the study population and low response rates.

Figure 1. PRISMA flow diagram of included studies

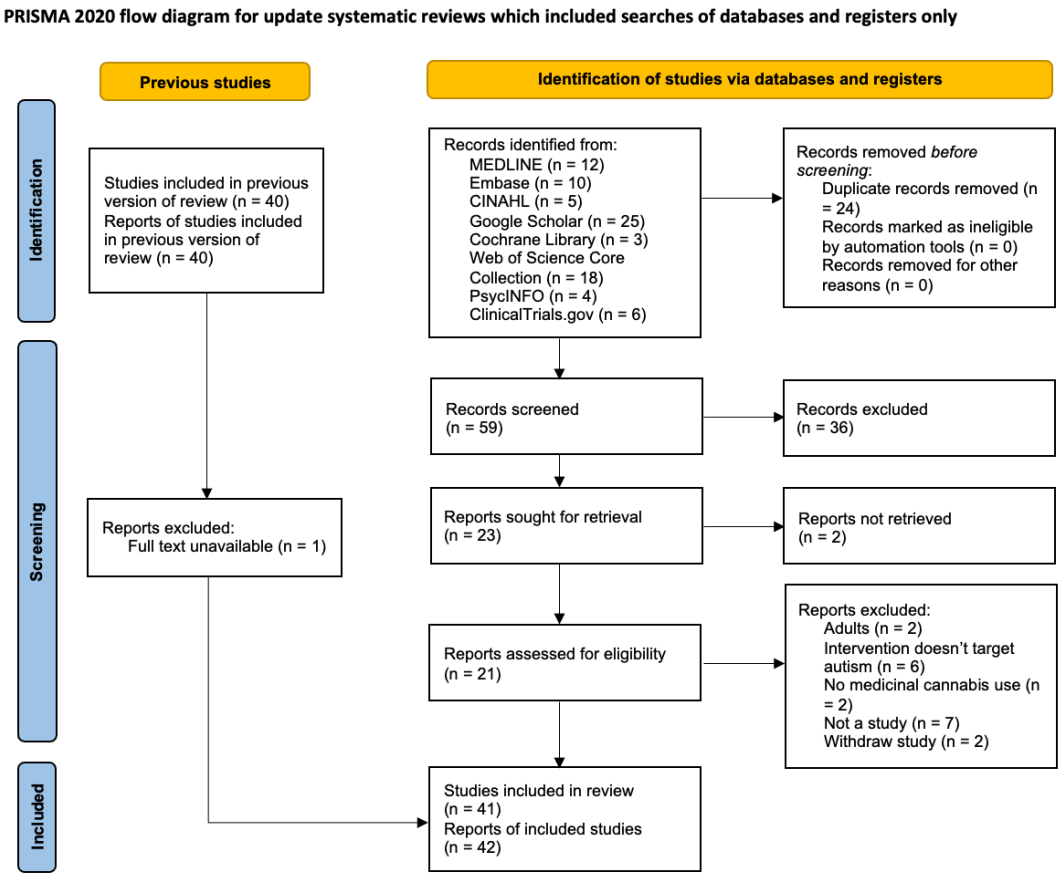


Table 1. Summary of included studies

Study type	No. of studies	Total participants
Single patient case report	7	7
Case series	3	20
Chart reviews	2	41
Cross-sectional surveys	6	2915
Qualitative interviews	2	35
Observational studies	9	602
Single arm trials	7	273

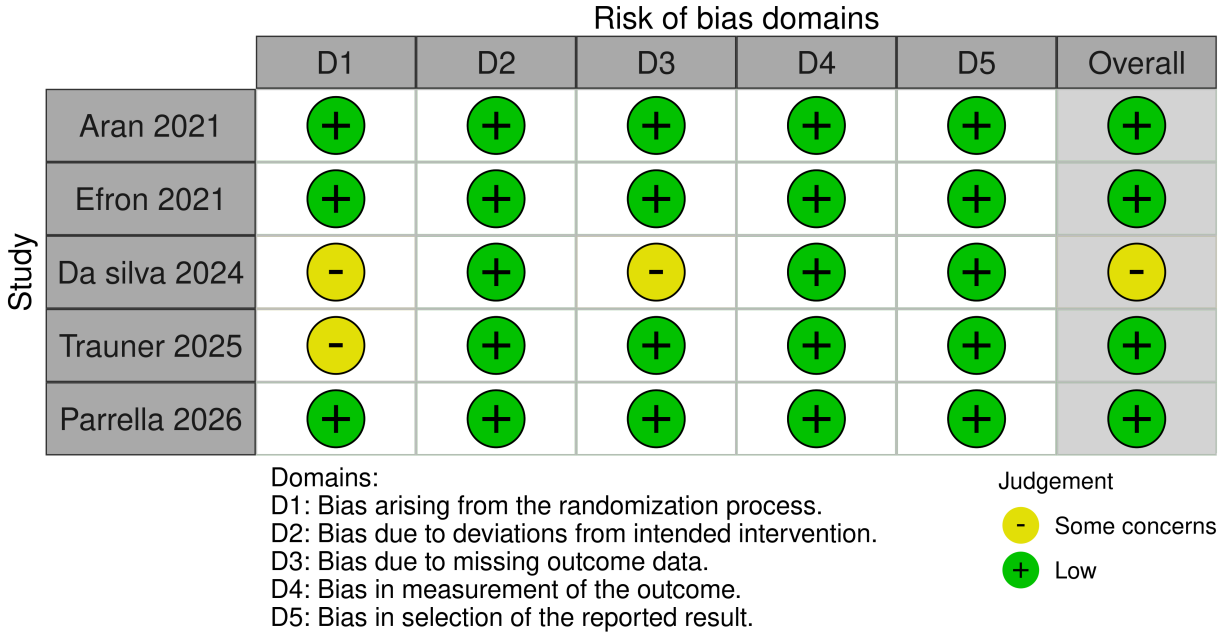
Randomized controlled trials	5	286

Quality assessment

Methodological quality varied across study designs. Non-randomized studies demonstrated moderate to high risk of bias. Case reports and case series were primarily limited by incomplete reporting of participant characteristics and post-intervention clinical outcomes. Cross-sectional surveys were generally at high risk of bias because of low response rates and insufficient descriptions of study participants. All non-randomized intervention studies were judged to have a high risk of bias owing to the absence of control groups. The two qualitative studies demonstrated low to unclear risk of bias. Complete methodological quality assessments for non-randomized studies are presented in Supplementary Figures 1-5.

The overall methodological quality of the included randomized controlled trials was high or moderate (Figure 2). Most studies demonstrated low risk of bias in key areas such as randomization procedures and outcome measurement. Two studies were judged as having some concerns, mainly related to the randomization process.[27,29] One of these studies also had concerns about missing outcome data due to patient withdrawal or loss to follow-up.[29] No studies were deemed to have a high risk of bias. Overall, the evidence from the existing randomized controlled trials was considered methodologically acceptable.

Figure 2. Summary of quality assessment of RCTs



Characteristics of RCTs

Five randomized controlled trials evaluated the effects of cannabinoid-based interventions on children or adolescents with autism (table 2).[25–29] Study designs included double-blind, placebo-controlled parallel trials and crossover trials with washout periods. Sample sizes varied widely, from small feasibility studies with only eight participants to large trials with up to 150 participants. Most studies recruited pediatric participants, but inclusion criteria differed: some studies specifically targeted children with autism[27], while others included children with intellectual disabilities[28] and severe behavioural problems[25,26,29], all of whom had autism.

Three studies evaluated purified CBD, including Epidiolex or 98% pure CBD oil, titrated to 5–20 mg/kg/day.[25–27] Other trials evaluated CBD-rich cannabis extracts or CBD/THC formulations, including formulations with CBD:THC ratios of 20:1 and 9:1.[28,29] Treatment durations ranged from 8 to 12 weeks, with crossover studies including washout periods of 4 to 8 weeks.

Outcome measures also vary, including caregiver-reported scales, clinician-assessed measures, and standardized autism or behavioural assessments such as the the Social Responsiveness Scale, Second Edition (SRS-2), Clinical Global Impression-Improvement scale (CGI-I), Home Situations Questionnaire-Autism Spectrum Disorder (HSQ-ASD), Repetitive Behavior Scale-Revised (RBS-R), Child Behavior Checklist (CBCL), Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), Autism Treatment Evaluation Checklist (ATEC), Aberrant Behavior Checklist-Irritability subscale (ABC-I), Autism Parenting Stress Index (APSI), Patient-Reported Outcomes Measurement Information System (PROMIS), Developmental Behavior Checklist, Second Edition (DBC-2), and Vineland Adaptive Behavior Scales.

Studies have shown that the efficacy of cannabinoids varies. Across the randomized trials, primary outcomes generally did not demonstrate consistent superiority over placebo.[25-29] Several studies reported signals in selected secondary or clinician-rated outcomes, but these findings were not consistent across measures.[25-29]

Table 2. Characteristic of randomized clinical trials of medical cannabis in children

Study	Sample size (N)	Group	Age (years)	Location	Cannabinoid intervention
Aran 2021[25]	150	Whole-plant extract, purified cannabinoids, and placebo (1:1:1; crossover design)	5-21; mean 11.8 (SD 4.1)	Israel	CBD: THC 20:1; purified CBD
da Silva 2024[29]	60	Cannabinoid n = 31; placebo n = 29	5-11; mean 7.7 (SD 1.7)	Brazil	CBD: THC 9:1
Efron 2021[26]	8	CBD n = 4; placebo n = 4	8-16; median 13.5	Australia	Purified CBD

Trauner 2025[27]	39	Participants received CBD and placebo in a crossover design	7-14	United States	Purified CBD
Parrella 2026[28]	29	Participants received CBD oil and placebo oil in a crossover design	5-12; mean 9.6 (SD 2.1)	Australia	CBD-enriched oil

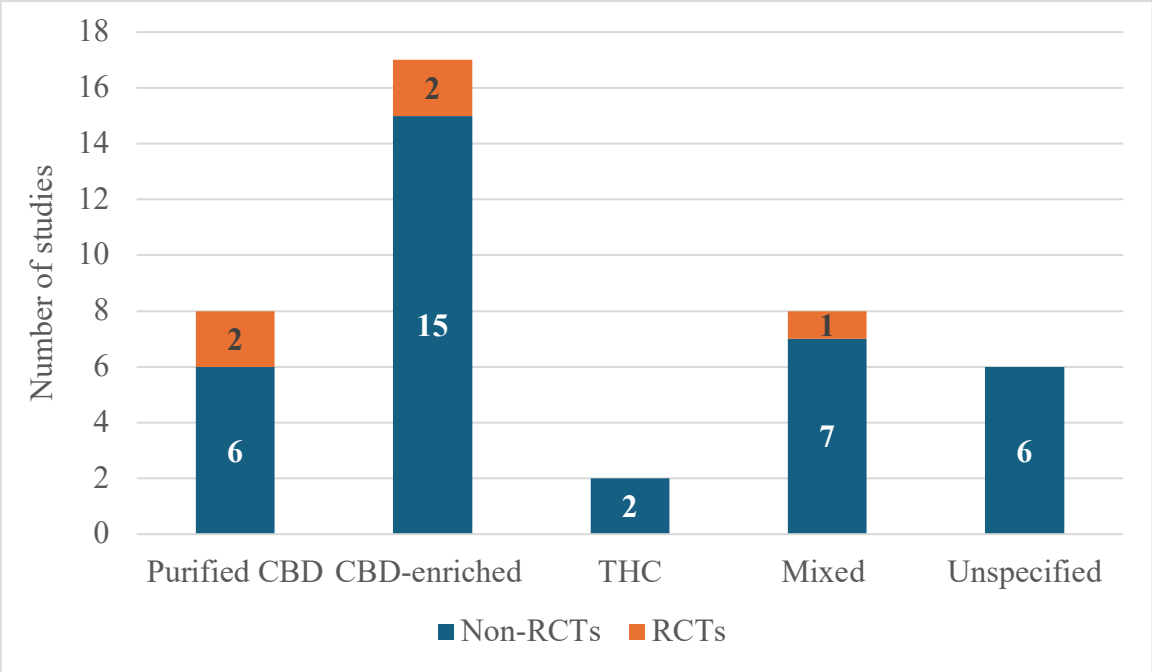
Dosage and routine

Most studies used CBD-dominant formulations, typically in the form of CBD-rich cannabis extracts with varying CBD:THC ratios. Figure 3 shows that CBD-rich formulations were clearly dominant in the included studies, while purified CBD, blended formulations, and products with high THC content were less frequently mentioned. Furthermore, a significant number of studies were categorized as "not clearly stated," reflecting the variability and incompleteness in cannabinoid component reporting in the literature. Detailed study characteristics are shown in Supplementary Table 1.

Common CBD:THC ratios were 20:1, 100:1, and 75:1, with numerous cases using almost pure CBD extracts. However, there are also reports of products with balanced ratios or high THC, and even pure THC products with lower ratios. Dosing regimens vary from fixed daily doses to weight-based regimens, with CBD dosages typically ranging from low milligram levels (4-20 mg/day) to high doses (up to 10-20 mg/kg/day). In most cases, the dosing regimen is adjusted continuously based on the situation.

The primary route of administration is oral, including oils, capsules, and edible products; sublingual, topical, or inhaled formulations are also occasionally used. Dosing frequency ranges from once daily to multiple times daily (twice or three times daily), and treatment duration varies from short-term trials of a few weeks to long-term observational follow-ups of several months over many years.

Figure 3. Distribution of cannabinoid formulations across included studies.

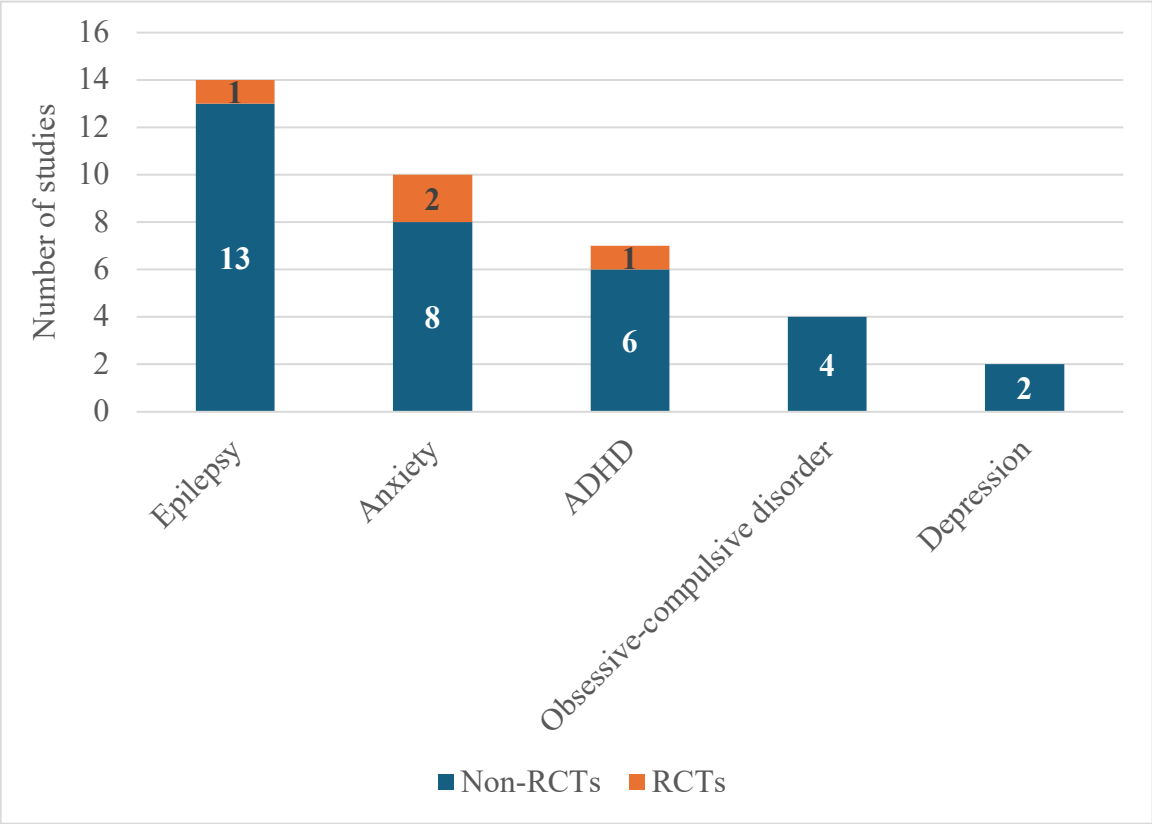


Footnote: Each study is counted only once, based on the unit of analysis. "Mixed" indicates that the same study evaluated more than one different product or formulation type. "Unspecified" indicates that insufficient information was available to classify the cannabinoid formulation.

Comorbidity

Comorbidities were commonly reported among children included in the reviewed studies. Many participants had multiple coexisting medical or neurodevelopmental conditions in addition to autism spectrum disorder. Figure 4 summarizes the most frequently reported comorbidities across the included studies. These comorbidities include attention deficit/hyperactivity disorder (ADHD) related symptoms[3,26,50,52,58,64,75], and various type of seizure[3,27,35,53,55,58,59,61,62,71,72]. Other reported comorbidities included feeding difficulties, sleep disturbances, and general functional impairments.[71]

Figure 4. Most frequently reported comorbidities



Footnote: Only studies reporting comorbidities were included. Studies reporting more than one comorbidity category were counted multiple times.

Efficacy

Of the 41 studies included, a wide range of outcome measures were reported, but the measures and reporting methods varied considerably. Outcome measures related to social communication and autism-related characteristics were among the most frequently reported areas, including social interaction, social responsiveness, communication skills, language development, speech, and restricted or repetitive behaviors.[1–6,8,10,12,13,16–19,30,31,42] Behavioural outcomes typically included aggression, irritability, restlessness, hyperactivity, destructive behavior, and self-injury.[1–5,10,11,13–17,19]

The studies also reported outcome measures related to common comorbidities in children with autism. Common comorbidities were reported to be more frequently associated with seizures and epileptic seizures, attention deficit/hyperactivity disorder symptoms, feeding difficulties, sleep disturbances, anxiety, mood symptoms, and general functional impairment.[3,26-29,35,50-59,61,62,64,71,72,75] Other areas included cognitive and attentional functioning, adaptive functioning, quality of life, caregiver burden, parenting stress, and reduce using other

medications. [28,29,54,55,58,60–63,72] Some studies also reported physiological outcome measures such as appetite, eating behavior, physical activity, pain, and overall health.[26,29,35,54,58,61,62,72]

A variety of outcome instruments were used across studies, including standardized scales such as the Social Responsiveness Scale (SRS), Autism Treatment Evaluation Checklist (ATEC), Aberrant Behavior Checklist (ABC), Developmental Behaviour Checklist (DBC), Childhood Autism Rating Scale (CARS), Home Situations Questionnaire-ASD (HSQ-ASD), Clinical Global Impression scales (CGI), and caregiver-reported questionnaires.[25-29,37,50-57,63,67,71,72,76] However, significant heterogeneity existed in study design, outcome definition, assessment tools, and reporting methods. Therefore, the summary of existing evidence primarily employed descriptive methods rather than quantitative comprehensive analysis.

Observational studies and case reports could not determine efficacy; therefore, efficacy results were conducted across five controlled trials. Table 3 lists the main findings, which are significantly different from the control group. Overall, the results were mixed and varied depending on the outcome measures assessed. Among the five controlled trials, predefined primary outcomes frequently failed to demonstrate significant differences between cannabinoid treatment and placebo. In the study by Aran et al., no significant differences were identified using the Home Situations Questionnaire-ASD (HSQ-ASD), although greater improvement was observed using the co-primary Clinical Global Impression-Improvement scale (CGI-I). Parrella et al. found no significant differences in the primary SRS-2 outcome. Similarly, Trauner et al. reported no significant differences between treatment groups using the Child Behavior Checklist (CBCL), and ADOS-2. Da Silva Junior et al. also found no significant differences in ATEC and CARS scores. Efron et al. conducted a pilot feasibility trial and did not perform formal efficacy analyses. Descriptive data suggested greater reductions in irritability and parental stress scores in the cannabinoid group compared with placebo.

Improvements were more commonly observed in secondary or exploratory outcomes. Aran et al. reported improvement in social responsiveness measured using the SRS-2. Parrella et al. demonstrated improvements in social functioning using the PROMIS Social scale, social relating using the Developmental Behavior Checklist-2 (DBC-2), anxiety symptoms using the DBC-2 anxiety subscale, and parental stress using the Autism Parenting Stress Index (APSI). In Da Silva Junior et al., caregiver-reported assessments suggested improvements in psychomotor agitation, concentration, social interaction, and anxiety. In the pilot study by Efron et al., descriptive findings suggested greater reductions in irritability measured using the Aberrant Behavior Checklist-Irritability subscale (ABC-I) and improvements in APSI scores in the cannabinoid group. Trauner et al. did not demonstrate significant differences in predefined outcome measures; however, blinded clinical assessments suggested possible improvements in aggression, hyperactivity, communication, self-injurious behaviors, and anxiety in some participants.

Across the controlled trials, outcome measures varied considerably, limiting direct comparisons between studies.

Table 3. Outcome domains assessed across controlled trials of cannabinoid-based interventions in autism

Outcome domain	**Aran 2021[25]**	**da Silva 2024[29]**	**Efron 2021[26]**	**Trauner 2025[27]**	**Parrella 2026[28]**
Primary outcome Primary outcome measures	Mixed HSQ-ASD; CGI-I	Not significant ATEC; CARS	NA no formal efficacy analysis	Not significant RBS-R; CBCL; ADOS-2	Not significant SRS-2
Irritability	✓	✓	✓	✓	NR
Aggression	NR	✓	✓	✓	NR
Disruptive behavior	✓	✓	✓	✓	—
Social functioning	✓	✓	✓	✓	✓
Anxiety / Mood	NR	✓	NR	✓	✓
Attention	NR	✓	—	—	—
Child quality of life	NR	NR	✓	NR	—
Parent quality of life	—	NR	✓	NR	✓
Eating / physical outcomes	NR	✓	NR	NR	NR

Footnote: "✓" indicates a reported improvement signal, including statistically significant between-group findings or descriptive/exploratory improvements; "—" indicates that no improvement was demonstrated; NR indicates that it was not reported, and NA indicates that no formal efficacy analysis was conducted.

Safety

Adverse events associated with cannabinoid use in children with autism were commonly reported in observational studies and single-arm intervention studies.[3,25–27,35,50–63,71,72] Structured reporting was more frequently used to document adverse events in clinical studies compared to efficacy outcomes, but substantial differences in reporting criteria, adverse event definitions, and severity grading remain across studies.

Across the evidence base, the most frequently described adverse events involved the central nervous system and gastrointestinal system.[3,27,35,50–63,71,72] Commonly reported events included somnolence, drowsiness, sedation, agitation, irritability, restlessness, sleep disturbances, appetite changes, nausea, constipation, dry mouth, and nonspecific gastrointestinal symptoms. Less commonly reported events included fatigue, weight changes, respiratory symptoms, ocular symptoms, and urinary symptoms.[25–27,29,35,50,58,59,62] Most adverse events were described as mild to moderate and transient. Serious adverse events were uncommon but included psychosis,

mania, and worsening behavioural symptoms, particularly in studies involving high THC exposure and in case reports or case series.[57,59,67,73]

Safety results were assessed more systematically in five controlled trials (Table 4). Overall, cannabinoids were well tolerated during short-term treatment, and serious treatment-related adverse events were uncommon. No serious treatment-related adverse events were reported in controlled trials, except for one participant in Parrella et al. who discontinued treatment because of gastrointestinal discomfort. The most frequently reported adverse events in the controlled studies included somnolence, gastrointestinal symptoms, changes in appetite, insomnia, irritability, behavioural deterioration, and fatigue. However, adverse events were also reported in the placebo group, highlighting the importance of controlled comparisons when interpreting safety results. Due to the small sample sizes and relatively short follow-up periods, conclusions regarding long-term safety are limited.

Table 4. Adverse events reported in randomized controlled trials of cannabinoids in children with autism

Study	Adverse events	Cannabinoid arm(s)		Control arm
Aran 2021 [25]	Somnolence	26/95 (WPE)	22/93 (PC)	7/94
	Decreased appetite	23/95	20/93	14/94
	Weight loss	11/95	12/93	4/94
	Tiredness	24/95	32/93	18/94
	Euphoria	19/95	18/93	12/94
	Anxiety	19/95	25/93	13/94
da Silva 2024[29]	Dizziness	1/31		0
	Insomnia	1/31		0
	Abdominal pain	1/31		0
	Weight gain	1/31		0
Efron 2021 [26]	Eyes: Rolled up	1/4		0
	Tics/ grimace	1/4		0
	Ear ringing	1/4		0
	Headache	0		1/4
	Drooling/pooling	1/4		0
	Nose congestion/running nose	0		1/4
	Abdominal pain	1/4		0
	Appetite: Decreased	1/4		0
	Appetite: Increased	1/4		1/4

	Constipation	1/4	0
	Weight: Decreased	1/4	0
	Weight: Increased	1/4	3/4
	Restlessness/pacing/can't sit still	1/4	0
	Jitter/jumpiness/nervousness	1/4	0
	Acne	1/4	0
	Urination incontinence*	1/4	0
	Crying/feelings of sadness	1/4	1/4
	Drowsiness/lethargy/sedation	1/4	0
	Sleep: Excessive	1/4	0
	Sleep: Insomnia	1/4	1/4
Parrella 2026[28]	Gastrointestinal discomfort	2/29	0
Trauner 2025[27]	Diarrhea	5/59 events	1/49 event
	Insomnia	5/59 events	3/49 events
	Elevated Liver Functions	3/59 events	0
	Increased Appetite	3/59 events	1/49 event
	Irritability	3/59 events	3/49 events
	Loose stools	3/59 events	0
	Skin Injury	3/59 events	1/49 event
	Vomiting	3/59 events	1/49 event
	Aggression	2/59 events	2/49 events
	Appetite lost	2/59 events	2/49 events
	Constipation	2/59 events	2/49 events
	Cough	2/59 events	0
	Emotional Problems	2/59 events	1/49 event
	Fever	2/59 events	0
	Hyperactivity	2/59 events	2/49 events
	Upper respiratory tract infection	2/59 events	0
	Viral infection	2/59 events	1/49 event
	Agitation	1/59 event	2/49 events
	Behavior Change	1/59 event	0
	COVID-19	1/59 event	2/49 events
	Deliberate self-harm	1/59 event	5/49 events
	Enuresis	1/59 event	0
	Increase Repetitive Behaviors	1/59 event	0
	Itchy skin	1/59 event	1/49 event
	Leukopenia	1/59 event	0

Personality Change	1/59 event	0
Rash	1/59 event	1/49 event
Sleep disturbed	1/59 event	1/49 event
Sleepiness	1/59 event	1/49 event
Voice Disturbance	1/59 event	0

Footnote: Abbreviations: WPE, whole-plant extract; PC, pure cannabinoids; CBD, cannabidiol. Adverse event frequencies are presented according to the original study. For Trauner et al., adverse events were reported as frequencies of occurrence, making it could not be calculating the proportion. *Urinary incontinence included reports of nocturnal enuresis.

2.5 Discussion

Research on the use of cannabinoids in children with autism has increased substantially in recent years.[25,27–29,50] This literature review synthesizes current evidence regarding the use of cannabinoids to manage symptoms in children with autism. Across the 41 included studies, improvements were reported across several behavioural and functional domains.[3,26,28,29,55,57–59,61,62,72] However, the evidence was dominated by non-randomized studies and varied substantially in study design, cannabinoid formulation, and outcome assessment.[25–29] These limitations prevent clear comparisons or conclusions regarding efficacy between different studies.[25,27,28] The lack of long-term follow-up limits conclusions about sustained efficacy and long-term safety.[25,26]

Non-randomized studies frequently reported improvement in irritability, sleep disturbance, anxiety, or social functioning.[3,25,26,29,56,57,59,62,72,81] These may represent genuine treatment responses, but they may also be influenced by caregiver expectations or concurrent changes in other treatments. Nevertheless, the reported improvements suggest that cannabinoids may have the potential for managing selected behavioural or emotional symptoms, helping to identify outcome measures worthy of evaluation in future trials.[4,37,60–62,74,75,77–81] Improvements in social functioning and caregiver stress were also described.[54,55,58,60–63,72] However, these results are inconsistent, and many studies relied on caregiver observations and allowed flexible cannabinoid dosing or changes to concomitant medications.[3,25,27,29,50,57,71,72,76] These factors may help explain why positive outcomes were reported more often in real-world studies than in blinded trials.[25,27,28,50] Together, these findings identify several clinically relevant treatment signals, but they do not establish efficacy because most studies lacked placebo comparison.

The randomized trials provided more conservative findings.[25–28] Prespecified primary outcomes generally did not show consistent benefit over placebo, although selected secondary measures suggested possible improvement in anxiety, disruptive behavior, or social functioning.[25–29] Differences between trials may partly explain this pattern. The trials evaluated purified CBD, CBD-rich cannabis extracts, and balanced CBD:THC formulations.[25–29] The dose and duration of exposure also varied.[25–28] These products may differ in pharmacological activity

and tolerability. They also assessed different types of clinical change. A significant secondary outcome may identify a promising treatment signal, particularly in a pilot study, but it does not provide the same level of evidence as a prespecified primary outcome. This distinction is especially important when primary and secondary outcomes are interpreted. The current evidence therefore provides the strongest preliminary support for further investigation of irritability, sleep disturbance, and anxiety as targeted outcomes.[25–29] Future trials should distinguish clearly between core autism-related outcomes and associated symptoms. Each trial should define a specific target symptom before treatment begins and select a primary outcome that directly reflects that target.

Clinical heterogeneity may also contribute to variation between studies. Autism differs widely in presentation, and the included participants had different levels of cognitive or communication ability.[2,87–89] Co-occurring conditions were common.[25,27,28,50] Epilepsy may influence both the decision to use CBD and the outcomes observed during treatment. Sleep improvement could indirectly reduce daytime irritability, while changes in anxiety could affect social functioning. ADHD may influence ratings of attention or hyperactivity. A response driven by improvement in one co-occurring condition may therefore be interpreted as broader improvement in autism.

In safety reports, the majority of adverse events were mild to moderate. Somnolence and sedation were among the most frequent, suggesting that changes in alertness should be monitored routinely during treatment.[25–27] Gastrointestinal symptoms were also common, while changes in appetite or weight were reported less consistently. Behavioural worsening, including increased irritability or agitation, was described in some studies and may be particularly important in children whose treatment is intended to reduce these same symptoms.

Several controlled trials reported adverse events in both cannabinoid and placebo groups.[25–29] This indicates that some symptoms may reflect background symptoms or expectations. However, the presence of an event in both groups does not exclude a cannabinoid-related effect. Interpretation should consider whether the event was more frequent or severe during cannabinoid treatment. Its timing in relation to treatment initiation or dose escalation is also important.

Polypharmacy may increase the risk of adverse effects and make it difficult to attribute an event to a specific treatment. Participants in several studies were receiving psychotropic or antiseizure medications at baseline.[4,25,36,50,57,59,62,79,80] Sedation, appetite change, or behavioural worsening may result from the cannabinoid product, an existing medication, or an interaction between treatments. Incomplete reporting of medication doses and changes during follow-up made these possibilities difficult to distinguish. Pharmacokinetic interactions may further alter exposure to either treatment.[94–96] While most studies conclude that cannabinoids are generally well-tolerated, reports of adverse events are highly inconsistent.[25,27,59,61–63]

Some rare but clinically significant psychiatric adverse events were described, including

mania and psychosis, particularly in case reports involving THC-containing products or high dosages.[35,73,75] However, the available trials were too small to detect uncommon adverse events reliably, and their follow-up periods were insufficient to assess long-term neurodevelopmental safety.[2,44,93] Therefore, evidence regarding the long-term safety of cannabinoids in children with autism remains insufficient and requires further investigation through larger, well-designed longitudinal studies.

Several limitations of this review should be considered. The included studies differed substantially in design and methodological quality, preventing quantitative synthesis. Therefore, most findings were summarized descriptively. The number of studies reporting improvement should not be interpreted as an estimate of efficacy because sample sizes and risk of bias varied considerably. Positive findings may also be overrepresented through publication or selective reporting, particularly among case reports and uncontrolled studies. In addition, incomplete reporting of cannabinoid composition and concomitant medication use limited comparisons across studies.

Future research should prioritize larger-scale, longer-term randomized controlled trials. Although several randomized trials have been conducted, significant differences in cannabinoid formulations, CBD/THC ratios, dosing regimens, treatment duration, and efficacy endpoints still limit direct comparisons between studies.[25–29,50] Increasing standardization will significantly improve the interpretation and comparability of efficacy and safety results. Particular attention should be paid to distinguishing between improvements in related behavioural symptoms and genuine changes in the core characteristics of autism.[25,27] Furthermore, conducting more research to explore long-term neurodevelopmental and neuropsychiatric safety is crucial, especially in children receiving multiple concomitant medications.

Overall, the current evidence identifies irritability, sleep disturbance, and anxiety as possible targets for future cannabinoid trials in children with autism. Short-term adverse events appear generally manageable, but sedation and gastrointestinal symptoms require routine monitoring, while behavioural worsening and rare neuropsychiatric events warrant particular attention. Therefore, cannabinoids should be used cautiously in this population until more consistent evidence from adequately powered trials becomes available.

2.6 Conclusion

Cannabinoids may have potential for managing selected associated symptoms in children with autism, particularly anxiety, irritability, and sleep disorders. However, randomized trials have not demonstrated consistent benefits on prespecified primary outcomes, and evidence for improvements in the core features of autism remains limited and inconsistent. Although most reported adverse events were mild to moderate, concerns regarding neuropsychiatric safety, polypharmacy, and long-term developmental effects remain unresolved. More large-scale, standardized, long-term randomized controlled trials are needed to better clarify the efficacy,

safety, and clinical role of cannabinoids in children with autism.

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Supplemental table 1. Characteristics of included studies and efficacy findings

Author, Clinical trial registry	**Study design**	**Sample size**	**Cannabinoids, dose, route, frequency**	**Outcome scales**	**Efficacy findings**
Gaillard 2019[37]	Case report	1	CBD oil 9-60 mg/day, sublingual, oral	ATEC	Improvements were observed across multiple domains, including sleep, anxiety, attention, behavioural regulation, and social functioning.
Kurz 2010[76]	Case	1	Dronabinol, 0.62-3.72	ABC	Reductions were observed in

	report		mg/day, oral		hyperactivity, lethargy, irritability, and stereotypic behaviors, with improvements in inappropriate speech.
Ma 2022[77]	Case report	1	CBD oil (CBD 20mg, THC <1mg), 1-5 mg/kg/day, oral	Non-standard clinical descriptions	Improvements were reported across multiple domains, including behavioural symptoms, appetite, communication, sleep, anxiety, and daily functioning.
Nogueira 2023[78]	Case report	1	CBD-enriched CHE (100%: 0.3% CBD: THC), 270 mg/day, Oral	Non-standard clinical descriptions	Improvement in autism symptoms, also more attentive, affectionate, less aggressive and organized
Nunes 2023[79]	Case report	1	CBDA-enriched CHE, (CBDA: THC 2:1), CBDV: 1.5 mg/day, THC: 0.6mg/day, oral	Non-standard clinical descriptions	Improvements in clinical condition, stabilized and calmer behavior, reduction in episodes of agitation, resulting in normal school routine
Ponton 2020[4]	Case report	1	CBD-enriched CHE (20:1 CBD: THC), Dose range CBD 4-20 mg/day, THC: 0.2 to 1 mg/day	Non-standard clinical descriptions	Positive effect of CBD enriched CHE on behavioural symptoms, anxiety, sleep, as well as social deficits
Raz 2022[80]	Case report	1	CBD-enriched CHE, 21.6 mg/day, Terpene-enriched CHE terpenes/cannabinoids: 0.15/2.5, 11.2 mg/day, oral	Non-standard clinical descriptions	Strong improvement in efficacy after replacing purified CBD oil with terpene-enriched CBD oil in child with autism
Al-Soleiti 2022[73]	Case series	3	Patient 1 CBD enriched CHE (THC<0.3%), 10 drops, Oral, BID; Patient 2 and 3 Vaporized cannabis (20% THC and 10% THC)	Non-standard clinical descriptions	Use of cannabis was associated with mania and psychosis
Anderson 2022[75]	Case series	2	CBD-enriched CHE (>98% CBD) 18 mg/day to 25 mg/day,	Non-standard clinical descriptions	Initial treatment was associated with worsening behavioural symptoms and no clinical benefit;

			oral, BID and CBD 50 CHE (50 mg CBD/ml and <0.2 mg THC/ml), 12.5 mg, Oral, BID		however, following dose adjustment, improvements were observed in communication, sleep, and anxiety.
de Souza Mazza 2022[74]	Case series	15	CBD and THC solution (100:1 CBD: THC), 1-5 mg/kg/day, oral, NR	Non-standard clinical descriptions	Improvements were observed across behavioural and cognitive domains, including reduced aggression and enhanced social cognition, communication, and learning.
DiLiberto 2022[65]	Cross-sectional survey	89	CBD-enriched CHE, purified CBD, oral, NR	Non-standard clinical descriptions	Caregiver-reported outcomes suggested moderate effectiveness for behavioural symptoms, with greater improvements in irritability observed at higher CBD doses (with low THC).
Fossi 2023[66]	Cross-sectional survey	50	Medical cannabis, unspecified, oral, NR	Non-standard clinical descriptions	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[67]	Cross-sectional survey	1276	Variety of products including CBD-containing products, THC, cannabis flowers, cannabis-based oils, edible cannabis products, Vape pens, tetrahydrocannabinol acid, and transdermal products	Qualitative thematic analysis, WHO Quality-of-Life assessment, Numeric Pain Rating Scale, Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index for adults, CSHQ-A for children	The majority of participants (77%) reported benefits of cannabis use. Improvements were observed in physical symptoms, mental health, and quality of life, with cannabis users reporting better sleep, reduced pain, anxiety, and depression compared with controls.
Schwaller 2023[64]	Cross-sectional survey	518	Unlicensed CBD products, Unspecified, oral	Non-standard clinical descriptions	Parents showed a higher preference for administering unlicensed CBD in children with GAD compared to ADHD and autism. Commonly used product types included oral formulations such as gummies and oils.

Sivori 2023[36]	Cross-sectional survey	454	Medical cannabis, unspecified, oral,	Non-standard clinical descriptions	A majority of caregivers expressed willingness to try cannabis for children with autism. Commonly targeted symptoms included attention difficulties, hyperactivity, anxiety, sensory sensitivities, and behavioural challenges.
Krauss 2022[68]	Cross-sectional survey	518	CBD products, unspecified, oral	Non-standard clinical descriptions	30.9% (n=162) of parent reported using CBD products in children with ADHD, GAD, and/or autism
Lane 2022[69]	Qualitative Interview	21	Medical cannabis, unspecified, oral	Non-standard clinical descriptions	Limited knowledge about cannabis uses in children with autism, while common source of information were Internet and social media
Shaw 2023[70]	Qualitative ethnographic interviews	14	Purified CBD, CBD enriched CHE (15:0.7, 1:20 CBD: THC), oral	Non-standard clinical descriptions	Common barriers to CBD use included cost, lack of evidence, limited access to reliable information, and concerns about adverse effects.
Aran 2019[57]	Retrospective feasibility study	60	CBD-enriched CHE (20:1), 1 mg/kg/day to 10 mg/kg/day, sublingual, BID or TID	A modified Liverpool Adverse Events Profile, CGIC, HSQ-ASD and APSI	Improvements were observed in global functioning, anxiety, communication, and behavioural symptoms based on standardized assessment scales.
Barchel 2019[59]	Prospective observational study	53	CBD-enriched CHE (20:1), CBD 16mg/kg (maximum dose 600 mg/day) and THC 0.8mg/kg (maximum dose 40 mg/day), oral	Non-standard clinical descriptions	Improvements were observed across behavioural and emotional domains, including hyperactivity, self-injury, sleep, and anxiety.
Bar-Lev Schleider 2019[58]	Retrospective observational	188	CBD-enriched CHE (30% CBD and 1.5% THC) and, mean CBD dose 79.5 ± 61.5 mg,	Non-standard clinical descriptions	Improvements were reported in symptom severity, quality of life, mood, sleep, functional independence, and concentration

	study		mean THC dose 4.0 ± 3.0 mg and 5.0 ± 4.5 mg THC/day (3% THC), oral, TID		following treatment.
Bilge 2021[60]	Prospective observational study	33	CBD-enriched CHE, mean CBD dose 0.7 mg/kg (range 0.3–2 mg/kg), maximum CBD 40 mg/day dose sublingual, BID	Non-standard clinical descriptions	Mixed outcomes were reported, with some improvements in behavioural symptoms, communication, cognition, and social interaction, while no change was observed in daily functioning in some patients.
Fleury-Teixeira 2019[61]	Observational Study	18	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, BID	Non-standard clinical descriptions	Patient reported median improvement in seizures >50%: Additional improvements were observed in behavioural, cognitive, sleep, and social functioning.
Kuester 2017[71]	Retrospective chart review	21	Balanced CBD THC product, high CBD, and High THC, oral,	CGI-I, APSI	Significant improvement in CGI-I and APSI scores 66.7% of patients. Improvements were also reported in core symptoms, including social communication, language, and repetitive behaviors.
Liz 2023[3]	Prospective observational study	27	CBD-enriched CHE, CBD 18.8mg/day, THC 1.3 mg/day, oral,	Non-standard clinical descriptions	Significant improvements were observed in core autism symptoms, including communication, social functioning, and repetitive behaviors. Additional improvements were reported in comorbid conditions such as ADHD, sleep, and feeding difficulties.
McVige 2020[97]	Retrospective	20	Medical cannabis, unspecified, oral,	CGI of Change (ACGIC) Scale measuring: QOL,	Significant improvements were observed in seizure frequency and

	chart review			activity limitations, symptoms, mood. A 10-point Likert scale measured: chronic pain change, epilepsy change; Secondary efficacies	severity, pain, sleep, mood, behavioural symptoms, communication, attention, and quality of life.
Montagner 2023[62]	Retrospective observational study	20	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	Non-standard clinical descriptions	High rates of improvement were reported across multiple domains, including quality of life, behavioural symptoms, communication, attention, and social functioning.
Nazareno 2023[63]	Retrospective open label study	113	CBD: THC product, unspecified, oral	CaGI-C	Caregiver Global Impression of Change scores were improved for behavior, sleep, and quality of life
Zürcher 2022[35]	Retrospective observational study	90	Dronabinol, Medical cannabis tincture, oil, CBD products (2.5%, 5%, 10%), oral,	Non-standard clinical descriptions	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
Hacohen 2022[50]	Non-randomized, single arm open-label trial	82	CBD-enriched CHE, maximum CBD dose 10 mg/kg/day (400 mg/day), and THC dose 0.5 mg/kg/day (20 mg/day), oral, NR	ADOS-2, Cognitive assessments: Wechsler Intelligence Scale; WPPSI, WISC or WAIS; Vineland adaptive behaviors scale, 3rd edition (Vineland-3), SRS-2	Improvements in restricted and repetitive behaviors were reported by caregivers, while no significant changes were observed in cognitive outcomes.
Kruger 2006[54]	Non-randomized open-label	10	Dronabinol, 5- 20 mg/day, oral, QD	SIB	Significant improvement in self-injurious behavior and mood/overall well-being.

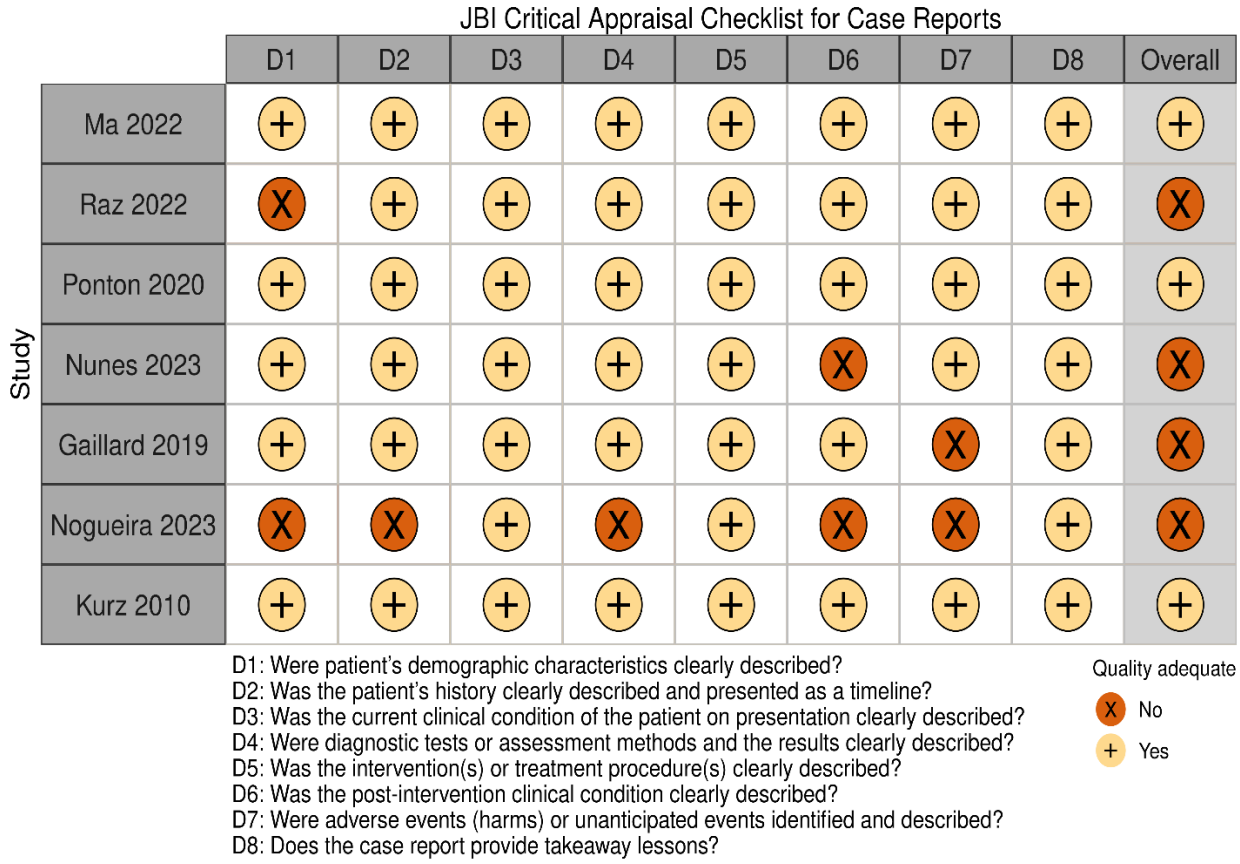
	trial				
Castellanos 2022, NCT03900923[52]	Open Phase 2 Trial	19	Purified CBD, 3 to 9 mg/kg/day, oral, NR	Primary: CGI-I, RBS-R, SRS-2, School-Age Form Score, ABC - Irritability Subscale Score, ABC - Social Withdrawal Subscale Score, ADAMS, SCARED-Parent Version Score, SDSC, VABS-Third Edition (Vineland-3), Parent/Caregiver Form, CGI-S, AFEQ, ASC-ASD-P, ASC-ASD-C - Child Version, OSU Autism Clinical Global Impressions, BIS, HSQ-ASD, SWAN	Approximately 40% of patients were classified as responders based on standardized measures, with overall improvement in symptom severity.
Heussler 2022[56]	Non-randomized open-label study	37	Purified CBD gel, 500 mg/day, topical, BID	ABC-C Irritability, PRAS-ASD, and APSI	Approximately 77% of patients showed improvement based on standardized measures, with additional improvements observed in anxiety, parenting stress, and irritability.
El-Sukkari 2023, ACTRN12621000760875 [53]	Open Label Study	18	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	Validated safety and clinical outcome measures, including laboratory monitoring and clinician- and caregiver-rated global and behavioural scales (e.g., CGI, ASC-ASD, SDSC)	Improvements were observed in overall symptom severity and behavioural symptoms. Reductions in anxiety were reported by some participants; however, findings were mixed, with some reporting increased anxiety and no significant improvement in sleep.
Scheffer 2021[55]	Non-randomized controlled trial	48	Purified CBD gel, based on weight 25 kg or less 250- 750 mg, >25 kg 500 - 1000 mg/day, topical, NR	Non-standard clinical descriptions	Reductions in seizure frequency were reported; however, findings were variable.

Stolar et al. 2022, NCT05212493[51]	Non-randomized open-label study	59	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	Biochemical analysis	No significant changes were observed in laboratory parameters following CBD administration.
Aran 2021[25]	Proof-of-concept randomized double blind placebo controlled cross-over trial	150	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 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, TID	HSQ-ASD, CGI-C, SRS-2, APSI, LAEP, CSHQ, Experience and Expectations Checklist	Mixed efficacy findings were observed. Significant improvements in clinician-rated disruptive behaviour and SRS-2 scores were reported with whole-plant extract compared with placebo, whereas sleep outcomes and several secondary measures showed no significant differences.
da Silva 2024[29]	Randomized, double-blind, placebo-controlled	60	CBD-enriched CHE, (9:1 CBD: THC), CBD: 0.9-21 mg/day, THC: 0.1-1.75 mg/day, oral, NR	semi-structured interviews, validated behavioural scales (ATEC), and laboratory-based safety assessments	Improvements were observed in psychomotor agitation, social interaction, anxiety, and concentration in children with mild autism. No significant improvements were found for aggression, speech, sleep, or overall autism severity scores.
Efron 2021[26]	Randomised placebo-controlled trial	8	Purified CBD, 5 mg/kg/day to 20 mg/kg/day, maximum CBD dose for > 50 kg 1000 mg/day, oral, NR	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,	Better improvements in irritability, anxiety, and caregiver-related outcomes were observed with CBD compared to placebo.

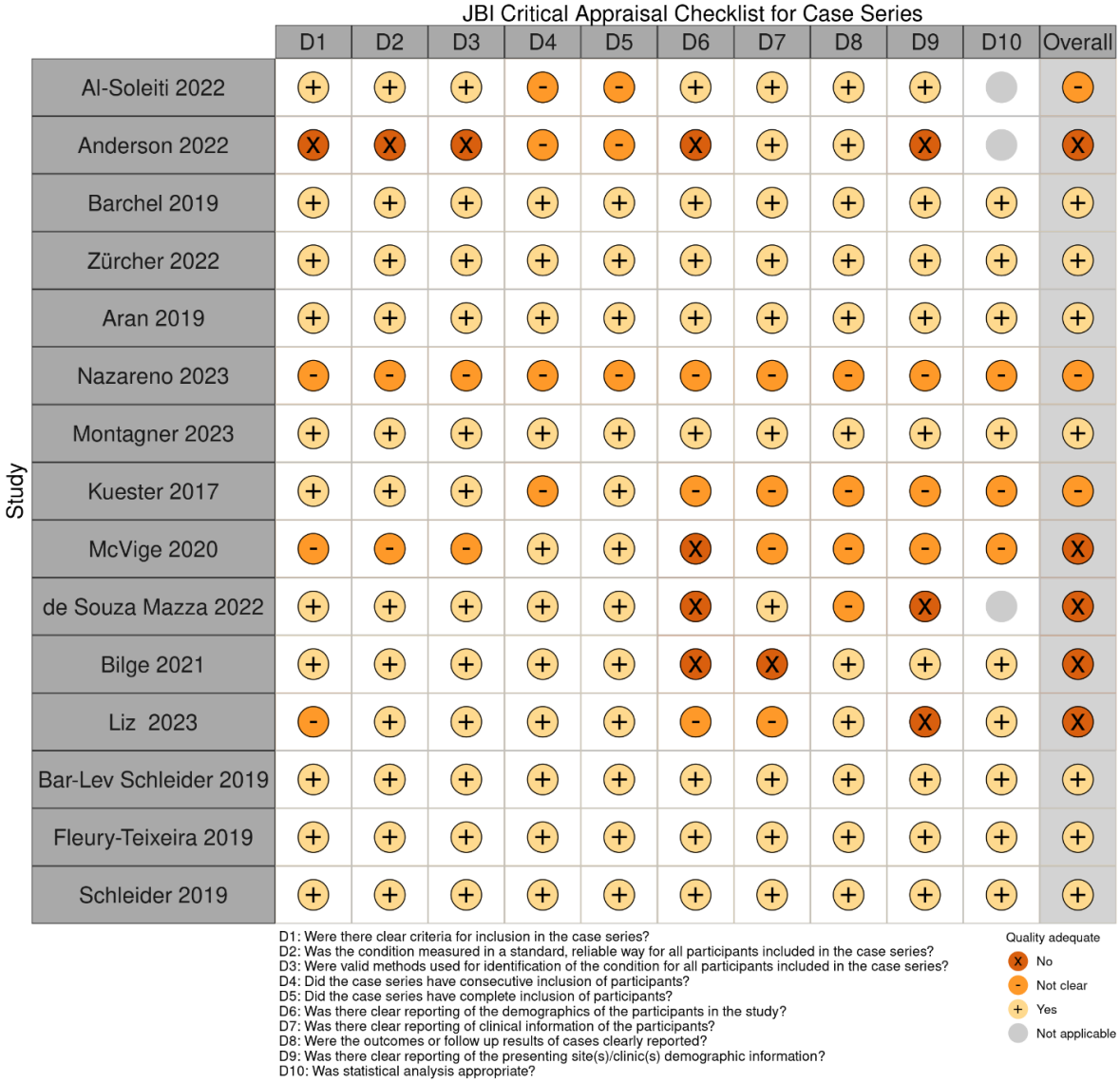
				Efficacy: Autism-Tics ADHD and Comorbidities, Social Communication Questionnaire, The ABC, Depression Anxiety Stress Scales, Child Health Utility 9D, AQoL, Beach Family Quality of Life, SDSC, Safety: Monitoring of Side Effects Scale	
Trauner 2025[27]	Randomized double-blind placebo-controlled crossover trial	39	Purified CBD, 5-20 mg/kg/day, oral, NR	Repetitive Behavior Scale-Revised, CBCL, ADOS- 2	Better improvements in aggression, hyperactivity, communication, repetitive behaviors, and anxiety were observed with CBD in some participants compared with placebo, although differences in primary outcome measures were not statistically significant.
Parrella 2026[28]	Randomized double-blind placebo-controlled crossover trial	29	CBD-enriched oil, 5–10 mg/kg/day, oral, NR	SRS-2, PROMIS Social/Anxiety/Sleep, DBC-2, Vineland-3, APSI, BRIEF-2, PedsQL, RBS-R, PWI-3	Better improvements in social relating, anxiety symptoms, and parental stress were observed with CBD compared to placebo, although no statistically significant differences were found for the primary SRS-2 outcome measure. Gastrointestinal discomfort was the main reported adverse event.

Footnote: “ABC-I”: Aberrant Behavior Checklist–Irritability; “APSI”: Autism Parenting Stress Index; “CGIC”: Caregiver Global Impression of Change; “CBD”: cannabidiol; “THC”: tetrahydrocannabinol; “CBDV”: cannabidivarin; “CHE”: cannabis herbal extract; “NR”: not reported; “QD”: once daily; “BID”: twice daily; “TID”: three times daily.

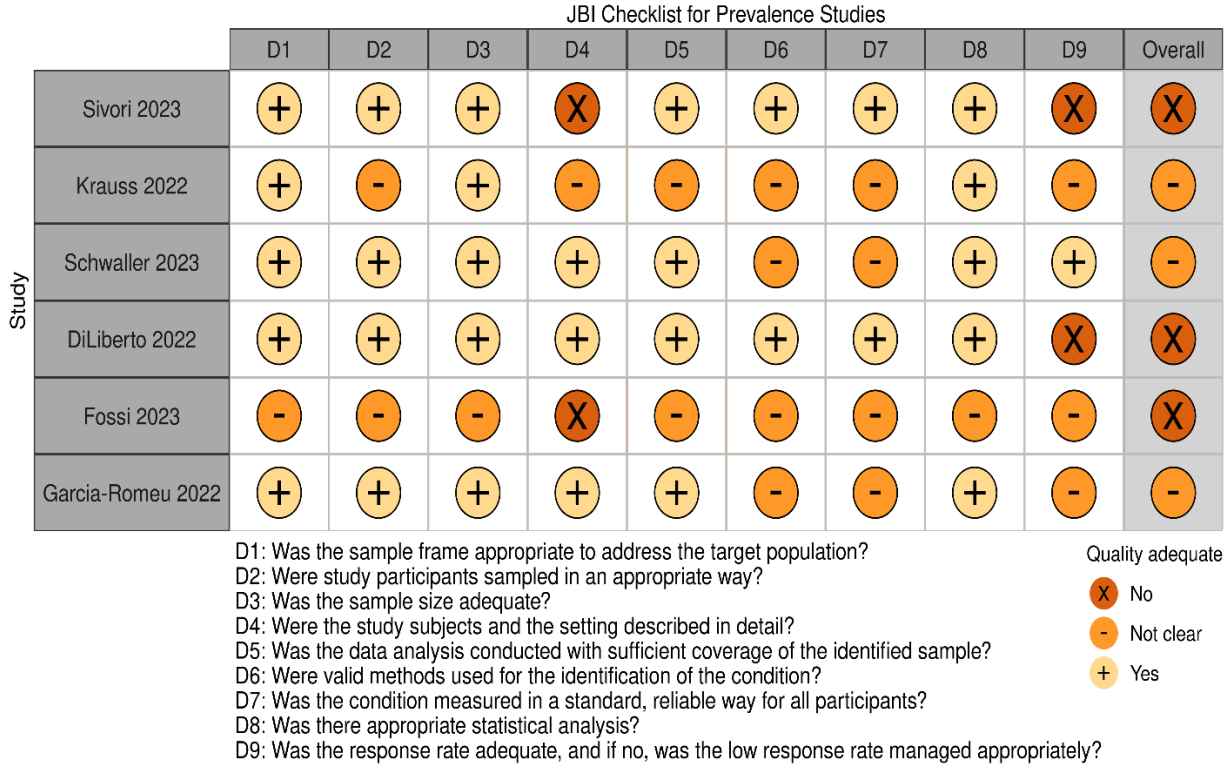
Supplemental Figure 1. Summary of quality assessment of included case reports



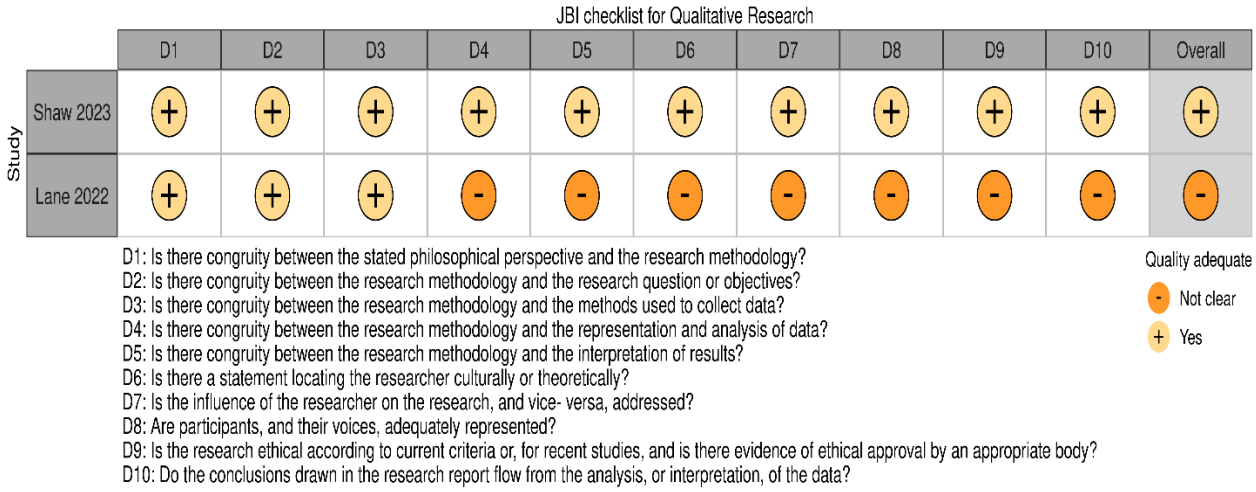
Supplemental Figure 2. Summary of quality assessment of included case series and treatment chart reviews



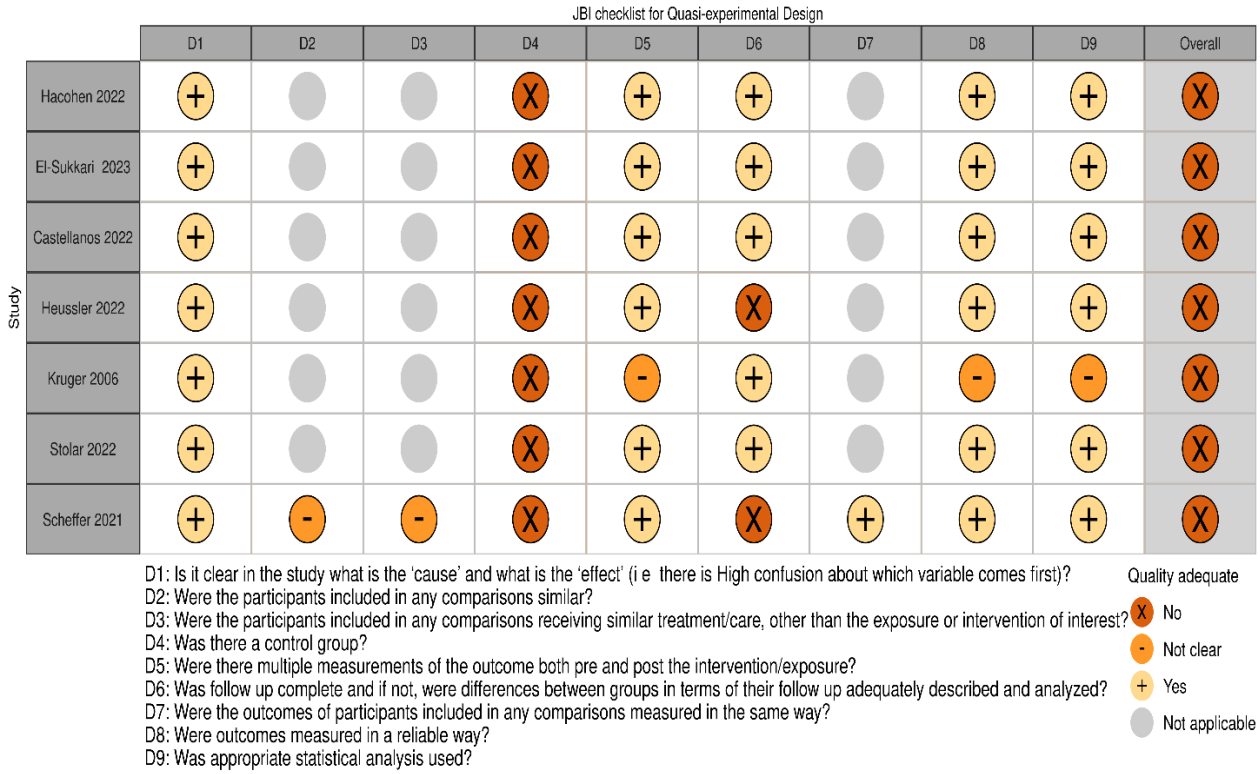
Supplemental Figure 3. Summary of quality assessment of included surveys



Supplemental Figure 4. Summary of quality assessment of included qualitative interviews



Supplemental Figure 5. Summary of quality assessment of included NRTs



Chapter 3: Perspectives from developmental pediatricians on medical cannabis in children with autism

3.1 Abstract

Background: Although high-quality evidence for medical cannabis in autism remains limited, discussions about its use are increasingly common in pediatric practice. We sought to understand Canadian developmental pediatricians' clinical knowledge, experiences and attitudes regarding medical cannabis in children with autism.

Methods: The survey was developed through literature review, expert panel consultation including parents, iterative revisions, and multidisciplinary validation to ensure content validity, clarity and relevance. Following ethics approval, we conducted a national cross-sectional electronic survey of Canadian developmental pediatricians. Email invitations and anonymous data capture forms were distributed via REDCap. Included responses were those from developmental pediatricians practicing in Canada. Storybooks were provided as incentives to participants who completed the survey and provide their mailing address.

Results: Of the 61 responses received, 38 eligible responses which met inclusion criteria were analyzed from 7 provinces and 2 territories. Most physicians (32/38, 84%) reported being asked about medical cannabis, most commonly once per year (19/38, 50%) or once per month (13/38, 34%). 2 participants had not been asked about medical cannabis but were aware of medical cannabis use; only 4 participants (4/38,11%) reported no prior discussions of medical cannabis use. When asking why medical cannabis had been discontinued, pediatricians reported that lack of perceived effectiveness (15/24, 63%) was most commonly reported. Some respondents (9/38, 24%) reported observing or knowing harms associated with medical cannabis use, including sedation, aggression, and sleepiness. When asked about potential benefits, the majority (26/38, 68%) were unsure. Interest in further research was high, with 84% (32/38) indicating they would likely support participation in a medical cannabis clinical trial. Most respondents reported no formal training in medical cannabis (28/38, 74%) and a lack of evidence-based pediatric-specific resources (37/38, 97%). Priority knowledge gaps were identified.

Conclusions: Medical cannabis is frequently raised by families in pediatric autism care, but developmental pediatricians in Canada report substantial uncertainty regarding its benefits, limited formal training, and a lack of evidence-based resources. Despite this, interest in research is high. These findings underscore the need for rigorous clinical research and targeted knowledge translation initiatives to address persistent evidence gaps.

3.2 Introduction

Cannabinoid-related products have become increasingly accessible in Canada following legalization[1] leading to growing clinical and public interest in their potential therapeutic applications across a range of medical conditions.[2] In pediatric populations, cannabinoids, particularly cannabidiol (CBD), have been most extensively studied in the treatment of seizures in children with Dravet syndrome, Lennox-Gastaut syndrome or tuberous sclerosis.[3–5] Clinical trials have demonstrated reductions in seizure frequency, leading to regulatory approval for specific indications.[6,7] Beyond epilepsy, cannabinoids are being explored for their potential effects on symptoms such as pain, sleep problems, anxiety, and neuropsychiatric disorders, contributing to expanding interest in their broader clinical applications.[8–11]

Within this broader context, there has been increasing interest in the potential role of cannabinoids in managing symptoms associated with autism.[12] Children with autism often experience behavioural challenges, sleep problems, and mood-related symptoms that can be difficult to manage with existing strategies.[13,14] Pharmacological treatment options are limited and may be associated with variable effectiveness and adverse effects, prompting some families and caregivers to seek alternative or adjunctive approaches.[15–17] In this context, medical cannabis has emerged as a potential option for symptom management.[12] Many studies have suggested that cannabinoids may provide improvements in those symptoms in children with autism.[18,19] Some observational and early clinical studies have reported reductions in irritability and even improvements in core symptoms of autism.[18–20]

However, the current evidence base supporting the use of medical cannabis in children with autism remains limited and heterogeneous.[17,21] Existing studies vary widely in study design, sample size, cannabinoid composition, dosing regimens, outcome measures, and clinical heterogeneity, which makes it difficult to draw definitive conclusions regarding effectiveness.[22,23] Safety concerns also persist, particularly with respect to potential impacts on neurodevelopment, long-term outcomes, and drug-drug interactions. These concerns are especially relevant for children with autism, who frequently have comorbid conditions and are often prescribed multiple medications.[24–26]

Despite uncertainly regarding safety and efficacy, clinical interest and family inquire of medical cannabis are increasing. Understanding physicians' perspectives in this evolving landscape is important for guiding clinical practice and future research. Developmental pediatricians play a central role in the care of children with autism and are frequently involved in decision-making regarding symptom management strategies.[27,28] In the absence of clear evidence-based recommendations, clinicians may be required to engage in discussions and decision-making under conditions of uncertainty.

To address these gaps, we conducted a national survey of developmental pediatricians in Canada to examine their experiences, attitudes, and perspectives about using medical cannabis in children with autism. The study aims to characterize clinical exposure, perceived benefits and harms, training and resource needs and areas of uncertainty, with the goal of informing future research priorities and guide knowledge translation efforts in this evolving area.

3.3 Methods

Materials and methods

We conducted a cross-sectional research design using an anonymous online questionnaire.

The questionnaire was developed based on previously published instruments assessing physicians' views on medical cannabis[29] and related literature addressing cannabis products, perceived effectiveness, and safety considerations. The questionnaire was adjusted to the context of medical cannabis use among children with autism.

Survey development involved and iterative process that included input from developmental pediatricians, clinical pharmacologists, parents of autism children and researchers with experienced in medical cannabis. Feedback from caregivers was included to improve the questionnaire's clarity and relevance. The questionnaire underwent multiple pilot tests with developmental pediatricians to assess its content validity, clarity, and fluency. Revisions were made based on pilot feedback.

The final questionnaire was reviewed by six experts before dissemination. The final questionnaire consisted of 24 questions and was designed to take approximately 20 minutes to complete.

Survey administration and dissemination

This survey was conducted using the Research Electronic Data Capture System (REDCap), a secure web-based platform for data collection.[30] Eligible participants were developmental pediatricians practicing in Canada and providing clinical care for children with autism. The list of eligible participants was obtained from the Canadian Pediatric Surveillance Project (CPSP).

Survey invitations containing a link to the online survey were sent via email. Up to four survey reminders were sent at two-week intervals to non-responders. Participation was voluntary and responses were collected anonymously. Data were automatically entered into a deidentified REDCap database. As a token of appreciation, participants who completed the survey were offered a children’s book; contact information for this purpose were not linkable to respondents to ensure the anonymity of the survey responses.

Statistical analysis and ethical approval

Descriptive statistical methods were used to summarize survey responses, including

frequencies and percentages of categorical variables. Responses to open-ended questions were analyzed using qualitative descriptive methods to identify common themes. This study has been approved by the Health Research Ethics Committee of the University of Manitoba. Completion of the survey constitutes implied consent.

3.4 Results

The survey was sent to 159 developmental pediatricians, and a total of 61 responses were received. Responses were excluded if the respondent lacked experience caring for children with autism, was not practicing in Canada, or provided insufficient data. After applying eligibility criteria, 38 responses from developmental pediatricians practicing in Canada with experience for caring autism children were included in this analysis.

Respondents represented physicians from 7 provinces and 2 territories. Years of clinical experience varied, with 39% reporting more than 20 years of experience and 24% reporting less than five years in practice. Most participants reported working in hospital-based clinics (24/38, 63%), followed by community-based settings (11/38, 29%) and private practice (4/38, 11%). The large number of them reported that their clinical role involved both diagnosis and follow-up care for children with autism (32/38, 84%) (Table 1).

Table 1. Characteristic of participating developmental pediatricians (N = 38)

Characteristic	Total N = 38	Percentage (%)
Province		
Alberta	7	18%
British Columbia	2	5%
Manitoba	4	11%
New Brunswick	1	3%
Newfoundland & Labrador	4	11%
Nova Scotia	1	3%
Ontario	13	34%
Québec	4	11%
Saskatchewan	2	5%
Years of experience		
0-5 years	9	24%
6-10 years	11	29%
11-15 years	0	0
16-20 years	3	8%
>20 years	15	39%
Practice setting		
Hospital-based	24	63%
Community-based	11	29%

Private	4	11%
Other	1	3%
Primary role		
Diagnosis	4	11%
Follow-up	2	5%
Both	32	84%

Clinical exposure to medical cannabis

Most respondents reported being asked about medical cannabis by families of children with autism (32/38, 84%). Among all respondents, inquiries occurred most commonly once per year (19/38, 50%) or once per month (13/38, 34%). Six respondents (16%) reported never being asked about medical cannabis.

When asked about clinical exposure, 28 respondents (74%) estimated that between zero and five children in their care had disclosed cannabis use for medical purposes in the past five years. Seven respondents (18%) reported more than ten children.

Among the developmental pediatricians who reported having been asked with or been disclosed to have children with autism using cannabis (n = 34), CBD-only products were the most commonly reported (19/34, 56%). High-CBD formulations were reported by 8 respondents (24%), and balanced THC/CBD products by 4 respondents (12%). Oral oils were the most frequently reported route of administration (22/34, 65%), followed by edible formulations (8/34, 24%) and sublingual administration (3/34, 9%) (Table 2).

Table 2. Clinical exposure to medical cannabis among developmental pediatricians.

VARIABLES	N (%)
Inquiry (N=38)	
Yes	32(84%)
No	6(16%)
Frequency of inquiry(N=38)	
Never	6(16%)
Once per year	19(50%)
Once per month	13(34%)
Once per week	0
Once per day	0
Children disclosing cannabis use in past 5 years(N=38)	
0-5	28(74%)
6-10	3(8%)
>10	7(18%)

Reported product types (N = 34)	
CBD only	19(56%)
High CBD product	8(24%)
Product unknown	8(24%)
Balanced THC/CBD	4(12%)
High THC	1(3%)
THC only	0
Routes of administration(N=34)	
Oral oils	22(65%)
Edibles (food or drink)	8(24%)
Sublingual	3(9%)
Smoke	2(6%)
Topical	1(3%)
Unknown	1(3%)
Suppository	0
Vaporizing	0
Not disclose	0

Note: One respondent reported “many” children disclosing cannabis use in past 5 years was included in ‘>10’. N=34 represents physicians with any clinical awareness of cannabis use among patients, defined as either being asked about medical cannabis use or having patients disclose cannabis use. Percentages for product types and routes of administration may exceed 100% due to multiple response options.

Perceived benefits and harms

Most respondents expressed uncertainty regarding the potential benefits of medical cannabis, with 68% (26/38) indicating that they were unsure. Equal proportions reported believing that medical cannabis has potential benefits (6/38, 16%) or no benefit (6/38, 16%).

A minority of respondents reported having observed harms associated with medical cannabis use. Overall, nine respondents (24%) reported any adverse effects. Among these, neuropsychiatric symptoms were the most commonly described (5/38, 13%), including sedation, aggression and sleepiness. Gastrointestinal symptoms, behavioural worsening, drug-drug interactions, and other concerns were each reported by a small number of respondents.

Among physicians who had any clinical awareness of cannabis use among patients (n = 34), 24 reported that their patients had stopped of use, while 10 reported that their patients continued use. The most common reason was lack of effectiveness (15/24, 63%). Adverse effects (5/24, 21%) and cost (5/24, 21%) were also frequently reported. Other reasons included pediatrician recommendation, other factors, taste aversion, and no longer needing the treatment (Table 3).

The use purpose most commonly reported by families included reductions in aggressive

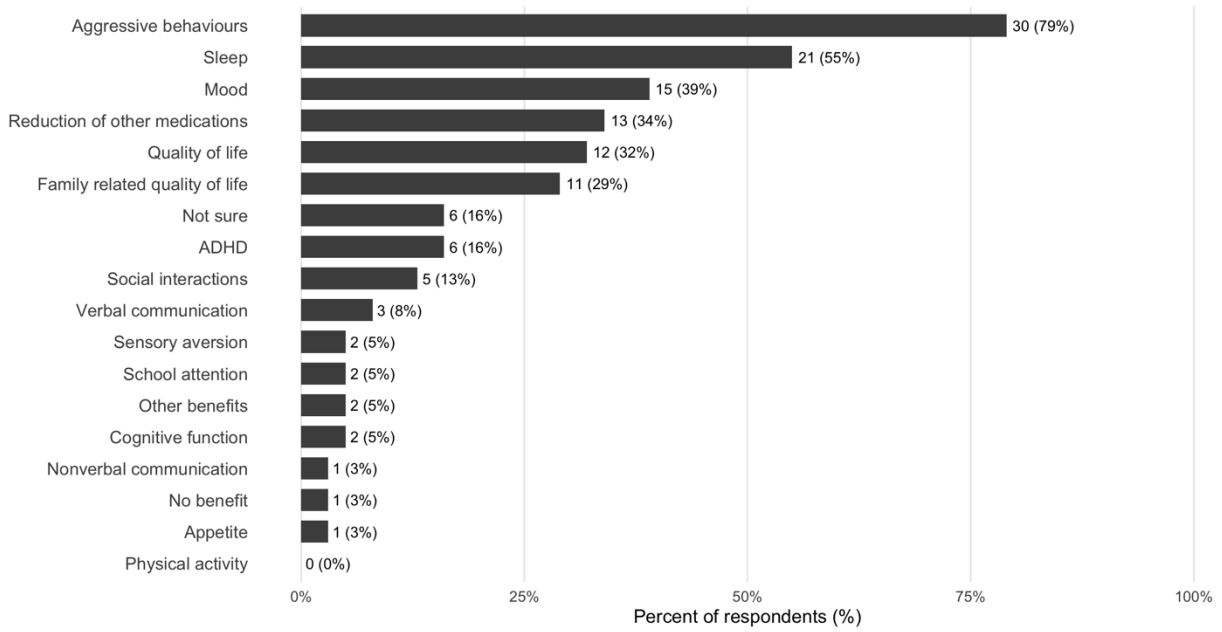
behaviors (30/38, 78%), sleep (21/38, 55%), mood (15/38, 39%), and reduction of other medications (34%, 13/38). Improvements in overall quality of life (12/38, 32%) and family-related quality of life (11/38, 29%) were also commonly hoped. Other reported areas of interest included ADHD symptoms (6/38, 16%), social interaction (5/38, 13%), and communication outcomes (4/38, 11%) (figure 1).

Table 3. Reported benefits, harms and reasons for discontinuation

Item	N	Percentage
Believe medical cannabis has any potential benefits (n = 38)		
Yes	6	16%
No	6	16%
Unsure	26	68%
Reported harms (n = 9)		
Neuropsychiatric symptoms	5	13%
Gastrointestinal symptoms	2	5%
Behavioural worsening	1	3%
Drug-Drug interaction	1	3%
Other concerns	1	3%
Did not report any harm	28	74%
Reasons for discontinuation (n = 24)		
Lack of effectiveness	15	63%
Adverse effect	5	21%
Cost	5	21%
Pediatricians' recommendation	3	13%
Other	3	13%
Taste aversion	2	8%
No need anymore	1	4%

Note: Multiple responses were allowed for perceived benefits; therefore, percentages may exceed 100%. Physicians reported harms or side effects of medicinal cannabis use (n = 9), and reasons for discontinuation were reported by physicians who indicated that patients had discontinued cannabis (n = 24).

Figure 1. Perceived benefits families hope to achieve among developmental pediatricians (n = 38)



Note: Multiple responses were allowed; therefore, percentages may exceed 100%.

Comorbidities and drug-drug interaction considerations

Over half of the respondents (22/38, 58%) typically considered comorbidities when assessing the feasibility of medical cannabis use in children with autism. Epilepsy was the most frequently mentioned comorbidity (18/38, 47%) with some noting that cannabis, particularly CBD, been used to treat refractory or treatment-resistant epilepsy. Pediatricians also reported that consideration of cannabis use was common in children with autism who also have epilepsy or genetic syndromes.

Respondents also described several clinical considerations related to variability in treatment among children with genetic disorders, potential pharmacokinetic differences and the need for specialist consultation, particularly with neurology. In addition, respondents frequently mentioned concerns about potential drug interactions. Medications commonly mentioned included antipsychotics, stimulants, selective serotonin reuptake inhibitors (SSRIs), antiepileptics, and alpha receptor agonists. Some respondents also emphasized drugs metabolized via the cytochrome P450 pathway. Sedative effects are frequently cited when used in combination with other medications, especially those with sedative properties.

Interest in clinical trials

Interest in future research was high. Many respondents (18/38, 47%) indicated that they would be very likely to discuss participation in a clinical trial evaluating the safety and effectiveness of medical cannabis for children with autism. Only a small proportion (5/38, 13%) reported that they would be unlikely to discuss such a trial. One respondent explicitly stated a

lack of willingness to participate based on concerns regarding safety.

Training, resources, and knowledge gaps

Most respondents reported limited training in medical cannabis. Only 26% (10/38) indicated having received any formal or informal training on the topic. Only one reported had access to pediatric-specific information. Similarly, only 11% (4/38) reported having received information related to the risks and benefits of medical cannabis use in children (Table 4).

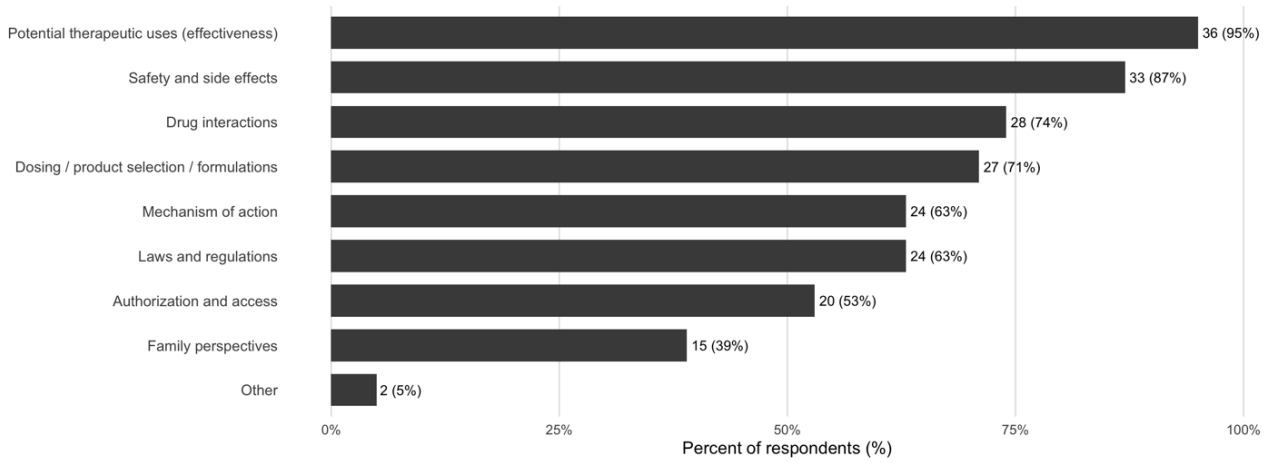
The most frequently reported areas of interest included mechanisms of action, effectiveness, drug interactions, dosing, product selection, and formulation. Additional topics included safety, access and authorization, and regulatory considerations (Figure 2).

Respondents indicated that families should be informed about the limited evidence base for medical cannabis use in children with autism. Key areas of uncertainty included effectiveness (36/38, 95%), potential risks (33/38, 87%), drug interaction (28/38, 74%), and dosing and product quality (27/38, 71%) was frequently reported. Many physicians noted that medical cannabis should not be started without prior discussion with a healthcare provider. The need for monitoring during use was also commonly described, particularly in situations where families may obtain products independently and product quality is uncertain.

Table 4. Training exposure and educational needs related to medical cannabis in children with autism (n = 38)

Training and resource awareness		
Question	**Yes n (%)**	**No n (%)**
Received any formal or informal training on medical cannabis	10(26%)	28(74%)
Information specific to pediatric populations	1(3%)	37(97%)
Information on risks and benefits of medical cannabis in children	4(11%)	34(89%)

Figure 2. Educational topics physicians would like to learn more about (n=38)

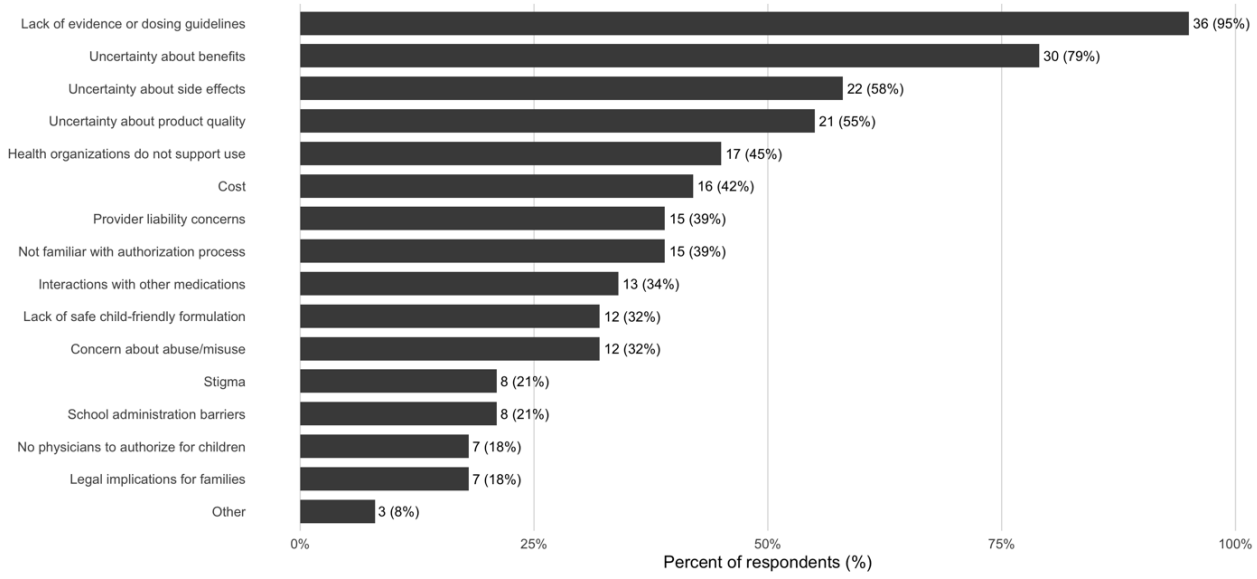


Note: Multiple responses were allowed.

Barriers to clinical use

Respondents reported multiple barriers, including uncertainty regarding benefits and side effects, lack of evidence-based clinical guidelines, concerns about product quality, and potential drug-drug interactions. Structural barriers such as lack of organizational support, unfamiliarity with authorization processes, and regulatory concerns were also reported (Figure 3).

Figure 3. Barriers to the use of medical cannabis in children with autism (n=38)



Note: Multiple responses were allowed.

Preferred sources of information

Respondents were asked to rank their preferred sources of information regarding medical cannabis. The Canadian Paediatric Society (CPS) was the most preferred source, followed by

peer-reviewed publications and conferences or workshops. Online portals and webinars or video lectures were ranked lower. Other sources such as the American Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics were also mentioned.

3.5 Discussion

In this national survey of developmental pediatricians in Canada, medical cannabis use in children with autism was frequently discussed in clinical practice. The response rate in this survey was close to the target outcome, but the possibility of no-response bias cannot be ruled out.[31] Physicians with stronger opinions or greater interest in medical cannabis were more likely to participate in the survey, which may limit the representativeness of the results.

There is still considerable uncertainty regarding its clinical application. Most respondents reported uncertainty about potential benefits and risks, drug-drug interactions, and the management of comorbidities, leading many to question its role in autism care. In addition, physicians reported limited access to training and pediatric-specific, evidence-based resources. Despite these gaps, interest in clinical trials was high.

These findings are consistent with previous survey-based studies among pediatric specialists[29], including pediatric oncologists and palliative care physicians, which have similarly reported increasing clinical interest in medical cannabis alongside substantial uncertainty regarding its effectiveness and safety. Prior studies have also identified limited training and lack of clinician confidence as key challenges in discussing and managing medical cannabis use in pediatric populations.

These highlight the gap for developmental pediatricians between clinical reality and the existing evidence base when having discussions about medical cannabis with families. Despite a lack of sufficient evidence to guide their practice, clinicians may still need to respond to inquiries from families regarding medical cannabis. In such situations, especially with children in complex clinical circumstances, physicians often must make decisions when the potential benefits and risks are uncertain. This can lead to variations in clinical practice, such as cautious avoidance, conditional acceptance, or reliance on specialist consultations without access to clear resources which outline the level of evidence available and potential risks. It is important for healthcare providers to recognize families' intentions when asking questions about cannabis-based products and focus on harm reduction strategies that prioritize maintaining an open relationship between the patient, family and care team.

Comorbidities and polypharmacy further complicate clinical decision-making given the potential for cannabinoids to interact with the metabolism of other drugs. Developmental pediatricians frequently expressed concerns about potential drug-drug interactions, particularly with commonly used psychotropic and antiepileptic medications, which might increase the

potential for additive sedative effects. Uncertainty around dosing, product quality, and long-term safety further reflects the absence of standardized clinical guidance. Many respondents emphasized that medical cannabis should not be initiated without prior consultation with a healthcare provider.

Importantly, limited clinical physician training and a lack of accessible evidence-based resources also pose obstacles. This can lead to families seeking guidance but receiving insufficient support from their primary healthcare teams, resulting in them making independent decisions without medical supervision. This may increase the risk of inappropriate or unsafe cannabinoid use, particularly among children.

In this context, well-designed clinical trials are needed to evaluate the safety and effectiveness of cannabinoids in children with autism. Future research should prioritize clinically meaningful outcomes, including behavior, sleep, mood, and quality of life, and incorporate longer-term follow-up to address key safety concerns such as neurodevelopmental effects and drug-drug interactions.

At the same time, knowledge translation strategies need to be developed to support clinicians and families. Improving access to evidence-based information helps facilitate informed decision-making and reduce reliance on non-medical sources. Furthermore, broader training on cannabis-related drugs should be provided so that pediatricians can quickly and comprehensively access the latest information and update their management strategies for children with autism in time.

In autism specifically, when designing a clinical trial, the heterogeneity of symptom presentation, variability in treatment response, and the high prevalence of comorbid conditions requiring concurrent medications warrant particular consideration during the design phase. Coordinated efforts from professional organizations, regulatory bodies, and research institutions may be needed to develop standardized guidelines, improve clinician training, and ensure access to reliable evidence-based information. These efforts are crucial to building research infrastructure to support safer use of medical cannabis among children.

This study provides national-level insight into developmental pediatricians' perspectives on medical cannabis use in children with autism. However, the modest sample size and potential response bias should be considered. In addition, findings reflect clinician perspectives and may not correspond to actual clinical outcomes experienced by individual patients or their families. Overall, medical cannabis remains an area of growing clinical interest but limited evidence in pediatric autism care.

3.6 Conclusion

In this national survey, developmental pediatricians reported substantial uncertainty

regarding the use of medical cannabis in children with autism, despite growing clinical interest and frequent consideration of its potential role in symptom management. Limited training and lack of pediatric-specific guidance remain important barriers to informed clinical decision-making. Future work should prioritize rigorous clinical trials, improved clinician education, and accessible evidence-based resources to support safer and more consistent care.

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Chapter 4: Adverse event profiles of medications used in children with autism: a real-world pharmacovigilance study

4.1 Abstract

Background: Medications are commonly used to support symptom management in children with autism; however, their safety profiles in real-world settings remain incompletely characterized. Pharmacovigilance data offer an opportunity to better characterize adverse event (AE) profiles across commonly prescribed drug classes. With growing interest in medical cannabis as a potential alternative, understanding existing AE profiles can help establish a reference for comparison.

Methods: A retrospective pharmacovigilance study was conducted using data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS; 2020-2025) and the European EudraVigilance database (2021-2025). Pediatric reports (aged <18 years) with autism were identified. Selected medications were grouped into seven classes: antipsychotics, ADHD medications, antidepressants (SSRIs), antiepileptics, anxiolytics, sleep agents and cannabinoid. AEs were extracted and categorized, with reporting frequencies and supplementary disproportionality analyses performed within each drug class.

Results: A total of 1,055 pediatric autism-related reports were identified from FAERS and 789 from EudraVigilance. Antipsychotics were the most frequently reported medication class, followed by ADHD medications. Across multiple medication classes, overlapping neuropsychiatric, metabolic, and neurologic adverse event patterns were observed. Prolactin-related events and weight-related problems were most frequently reported with antipsychotics and antidepressants, and extrapyramidal symptoms recurred across several medication classes. Supplementary disproportionality analyses supported the descriptive adverse event reporting patterns. Cannabinoid-associated reports remained limited (n=10), with agitation and insomnia among the most frequently reported adverse events.

Conclusions: Similar adverse drug event patterns were observed in both pharmacovigilance databases, with overlapping adverse events found across multiple psychotropic drug classes. In children with autism, the combined use of multiple medications can complicate drug safety assessments and adverse event monitoring. These findings support rigorous safety monitoring in this population when evaluating existing and emerging therapies.

4.2 Introduction

Autism is a heterogeneous neurodevelopmental disorder characterized by differences in social communication skills, restricted or repetitive behaviors, and sensory sensitivity.[1] These symptoms can significantly affect daily functioning and quality of life.[2] Management strategies are highly individualized because clinical presentation and improvement response vary

considerably between individuals.[3] Currently, pharmacological interventions for autism primarily target related symptom, with risperidone and aripiprazole approved by the U.S. Food and Drug Administration (FDA) for managing associated symptoms with autism.[4,5] Other psychotropic medications are also commonly prescribed for managing co-occurring symptoms and conditions.[6] However, adverse reactions remain a major clinical concern across multiple drug classes.[7,8] In addition, the frequent presence of comorbidities and polypharmacy may further increase the potential for drug interactions and clinical monitoring. [9,10]

Pharmacovigilance databases offer an opportunity to study adverse event reporting patterns in real-world situation. They help identify different safety patterns, including uncommon safety issues and potential signals requiring further investigation. In autism care, real-world safety data provide important information that is difficult to capture in controlled clinical trials because of complex medication use in routine clinical practice. Pharmacovigilance data helps establish baseline adverse event characteristics associated with commonly used medications and provides contextual information for evaluating emerging therapies in multi-medication use settings.

This study examined adverse event reporting patterns associated with commonly used medication classes in children with autism using two major pharmacovigilance databases, the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and EudraVigilance (EV).

4.3 Methods

Data sources and study design

A retrospective pharmacovigilance study was conducted using data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and the European EudraVigilance database. To improve data comparability and sample size, approximately five years of data were collected from both databases. FAERS data from the third quarter of 2020 through the second quarter of 2025 were downloaded and processed. EudraVigilance data from 2021 to 2025 were extracted using substance-based queries because this database does not offer quarterly download functionality. Despite this slight difference, both datasets cover approximately five years of reported data.

Case identification

Pediatric cases (aged <18 years) involving autism were identified in both databases. Autism cases were defined based on autism-related MedDRA preferred terms recorded in the indication field, including “autism”, “autism spectrum disorder”. Cases were deduplicated using CASEID in FAERS and EU Local Number in EudraVigilance, retaining the most recent version where applicable.

Drug classification

In FAERS, all reported drugs were extracted and separated at the case level, allowing a single case to contribute to multiple drug classes. Drug roles were classified as primary suspect (PS), secondary suspect (SS), or interacting (I), and all three roles were included in the analysis.

All reported drug names were cleaned and standardized before classification. Brand names and alternative spellings were mapped to a common generic or standardized drug name when possible. Medications were grouped into seven clinically relevant classes based on commonly used pharmacological treatments in children with autism and medical cannabis: antipsychotics, ADHD medications, antidepressants (SSRIs), antiepileptics, anxiolytics, sleep agents, and cannabinoids. The full drug-name mapping and class assignment rules are provided in Supplementary Table 2.

For EudraVigilance, commonly used medications were identified based on FAERS findings and expert input. Cases involving these active substances were extracted and classified using the same drug categories.

Adverse event identification and classification

Adverse events (AEs) were extracted at the preferred term (PT) level. In FAERS, only AEs associated with drugs classified as PS, SS, or I were included. Each case was assigned to one or more drug classes depending on reported medications.

To improve clinical interpretability, selected AEs were grouped into clinically meaningful categories based on similar MedDRA preferred terms. For example, mood-related symptoms, weight-related problems, prolactin-related events, extrapyramidal symptoms, and gastrointestinal symptoms were defined using predefined term groupings. AEs that could not be meaningfully grouped were retained as individual preferred terms.

Exclusion criteria

Non-adverse event terms, including indications, for example, autism and ADHD, product use issues, and medication errors, etc. were excluded.

Data analysis

Calculate the frequency of adverse events in each drug class. Each adverse event is counted only once per case in each drug class. Percentages are calculated with the total number of cases in each class as the denominator. To ensure interpretability while capturing less frequent but clinically relevant events in smaller drug classes, AEs with a frequency of at least 3% within each class were retained. Descriptive analyses were performed to summarize characteristics, drug distributions, and AE profiles. All analyses were conducted using R (version 2025.09.2+401).

The most frequently reported adverse event categories identified through the descriptive frequency analysis were subsequently evaluated using the disproportionality analysis function available within the FDA FAERS Public Dashboard. This generated reporting odds ratios (RORs) and corresponding 95% confidence intervals for each drug-adverse event pair. This supplementary analysis was performed to provide additional context for signal detection.

4.4 Results

Characteristics

A total of 1,055 pediatric autism-related reports were identified in FAERS between 2020 and 2025, compared with 789 reports identified in EudraVigilance between 2021 and 2025 (Tables 1–2). In both databases, most reports involved male patients and school-aged children. In FAERS, males accounted for 81% of reports, while children aged 6–12 years represented the largest age group (48%). Similarly, in EudraVigilance, 79% of reports involved males, and children aged 3–11 years represented the largest age group (49%).

Most FAERS reports were submitted by healthcare professionals, consumers, or physicians, whereas EudraVigilance reports were predominantly submitted by healthcare professionals. Reports originated from multiple countries, with the United States accounting for the largest proportion of FAERS reports. Cannabis involvement was uncommon, identified in only 9 FAERS reports (1%) and one in EudraVigilance reports.

Table 1. Characteristics of FAERS reports involving children with autism (2020–2025).

Variable	Category	n (%)
Sex	Male	858 (81%)
	Female	160 (15%)
	Unknown	37 (4%)
Age group	0–5 years	107 (10%)
	6–12 years	511 (48%)
	13–17 years	437 (41%)
Reporter type	Health professional	332 (31%)
	Consumer	264 (25%)
	Physician	260 (25%)
	Lawyer	173 (16%)
	Pharmacist	18 (2%)
	Other / Unknown	8 (1%)
Reporter country	United States	546 (52%)
	Canada	86 (8%)
	Japan	50 (5%)
	Netherlands	48 (4%)

	Germany	47 (4%)
	Turkey	40 (4%)
	France	36 (3%)
	United Kingdom	32 (3%)
	Italy	27 (3%)
	Australia	21 (2%)
	Other	122 (12%)
Cannabis involvement	Cannabis involved	9 (1%)
	No cannabis involved	1046 (99%)

Footnotes: Data were extracted from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) between 2020 and 2025 and restricted to reports involving individuals aged <18 years with autism. Percentages represent the proportion of reports within the total study population (N = 1,055).

Table 2. Characteristics of adverse event reports from EudraVigilance reports involving children with autism (2021–2025)

Characteristic	Category	n (%)
Sex	Female	140 (18%)
	Male	627 (79%)
	Not Specified	22 (3%)
Age group	0-1 Month	69 (9%)
	2 Months - 2 Years	34 (4%)
	3-11 Years	387 (49%)
	12-17 Years	299 (38%)
Report type	Spontaneous	789 (100%)
Reporter qualification	Healthcare Professional	641 (81%)
	Non-Healthcare Professional	148 (19%)
Reporter country	European Economic Area	389 (49%)
	Non-European Economic Area	400 (51%)
Cannabis involvement	Cannabis involved	1
	No cannabis involved	788 (100%)

Footnote: Data were extracted from EudraVigilance between 2021-2025. Percentages are calculated based on the total number of unique cases included in the analysis (N=789). Only cases involving individuals aged <18 years with autism were included.

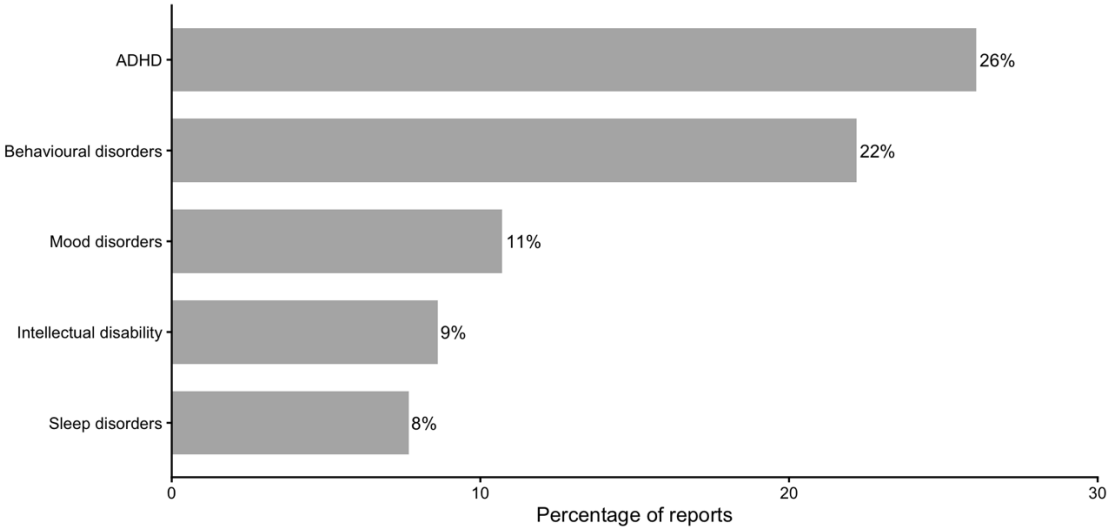
Comorbid conditions and medication-use patterns

Among pediatric autism-related reports in FAERS, attention-deficit/hyperactivity disorder (ADHD) was the most frequently reported comorbid condition (26%), followed by behavioural disorders (22%), mood disorders (11%), intellectual disability (9%), and sleep disorders (8%) (Figure 1). Multiple comorbid conditions could be reported within the same case.

Medication reporting patterns were broadly similar across FAERS and EudraVigilance (Figure 2a and Figure 2b). Antipsychotics were predominant medication class in both databases. Risperidone was the most frequently reported individual drug (FAERS: n=586; EudraVigilance: n=285), followed by aripiprazole (n=274 and n=157, respectively). Among ADHD-related and antidepressant medications, methylphenidate (FAERS: n=130; EV: n=62) and sertraline (FAERS: n=133; EV: n=45) were commonly represented in both systems. Quetiapine, clonidine, olanzapine, fluoxetine, melatonin, paliperidone, haloperidol, atomoxetine, lorazepam, and lamotrigine were also frequently reported across databases. Compared with FAERS, EudraVigilance demonstrated relatively greater representation of antiepileptic medications, particularly valproic acid (n=152). Cannabidiol-associated reports were uncommon in both databases (FAERS: n=9; EV: n=1).

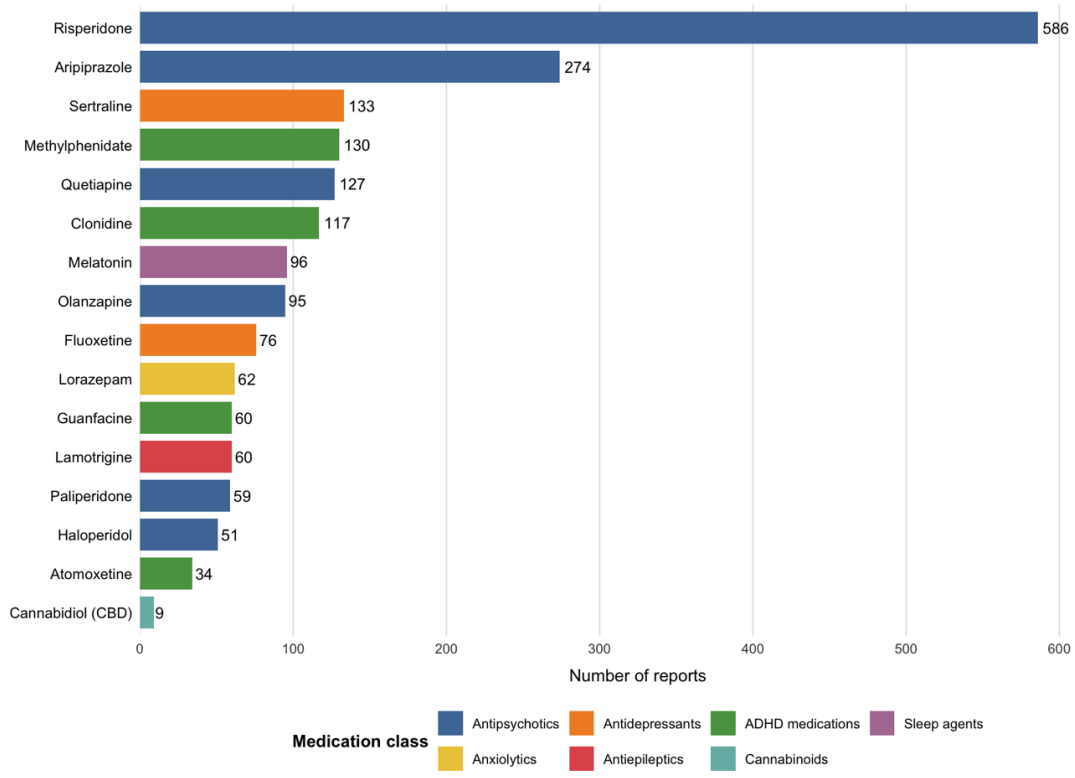
In addition to the frequent reporting of individual medications, multiple medication reporting was common in both databases. Among the 1,055 cases were included, median number of reported medications per case was 2 (interquartile range [IQR], 1–3) in FAERS. Similarly, among the 789 pediatric EV cases, the median number of reported medications per case was also 2 [IQR 1–3]. Polypharmacy was common across both databases, with more than half of the cases receiving two or more medications. Antipsychotics, ADHD medications, SSRIs, and antiepileptics are commonly co-reported (Figure 3a and 3c). Heatmap analyses demonstrated substantial overlap between psychotropic medication classes, particularly between antipsychotics and antidepressant medications, followed by combinations involving ADHD medications and antiepileptics (Figure 3b and 3d).

Figure 1. Most frequently reported comorbid conditions among pediatric autism cases in FAERS (2020-2025)



Footnote: Percentages are calculated based on the total number of cases (n = 1055). Multiple comorbidities per case were allowed. Data were derived from FAERS reports for individuals aged <18 years.

Figure 2a. Most frequently reported drugs in FAERS cases involving children with autism (2020–2025).



Footnote: Percentages represent the proportion of reports involving each drug. A single report may

include multiple drugs.

Figure 2b. Number of reports by individual drug among EudraVigilance case involving children with autism (2021-2025).

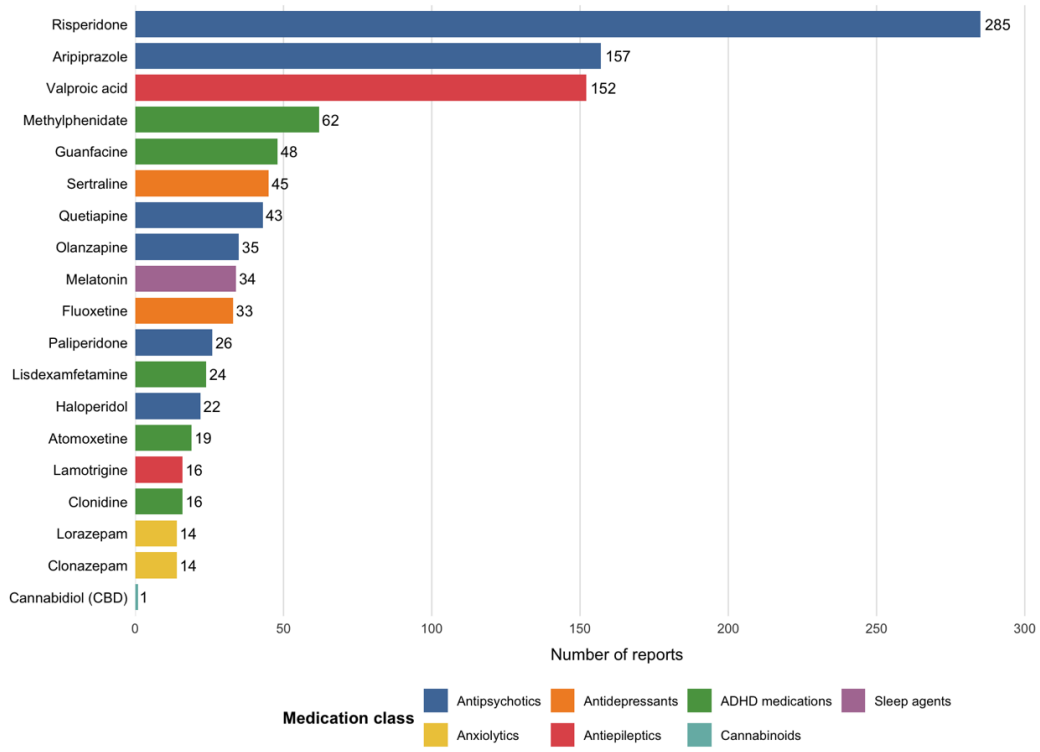


Figure 3. Polypharmacy burden and co-reported medication classes in pediatric autism-related pharmacovigilance reports

Figure 3a. Polypharmacy burden among pediatric autism-related FAERS reports (2020-2025).

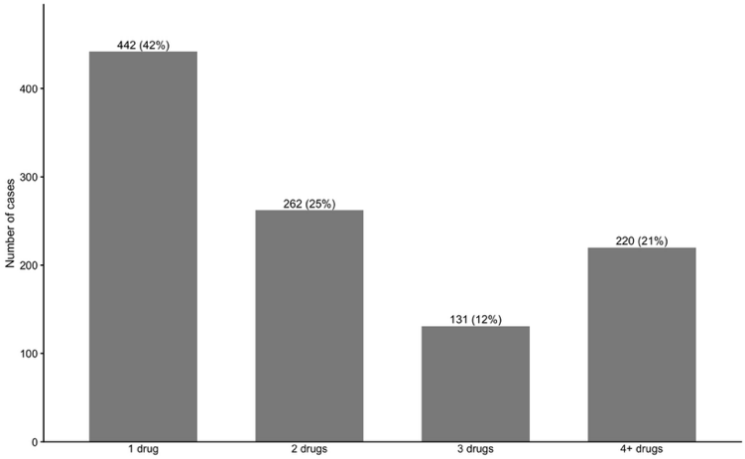


Figure 3b. Heatmap of co-reported medication classes in pediatric autism-related FAERS reports

(2020-2025).

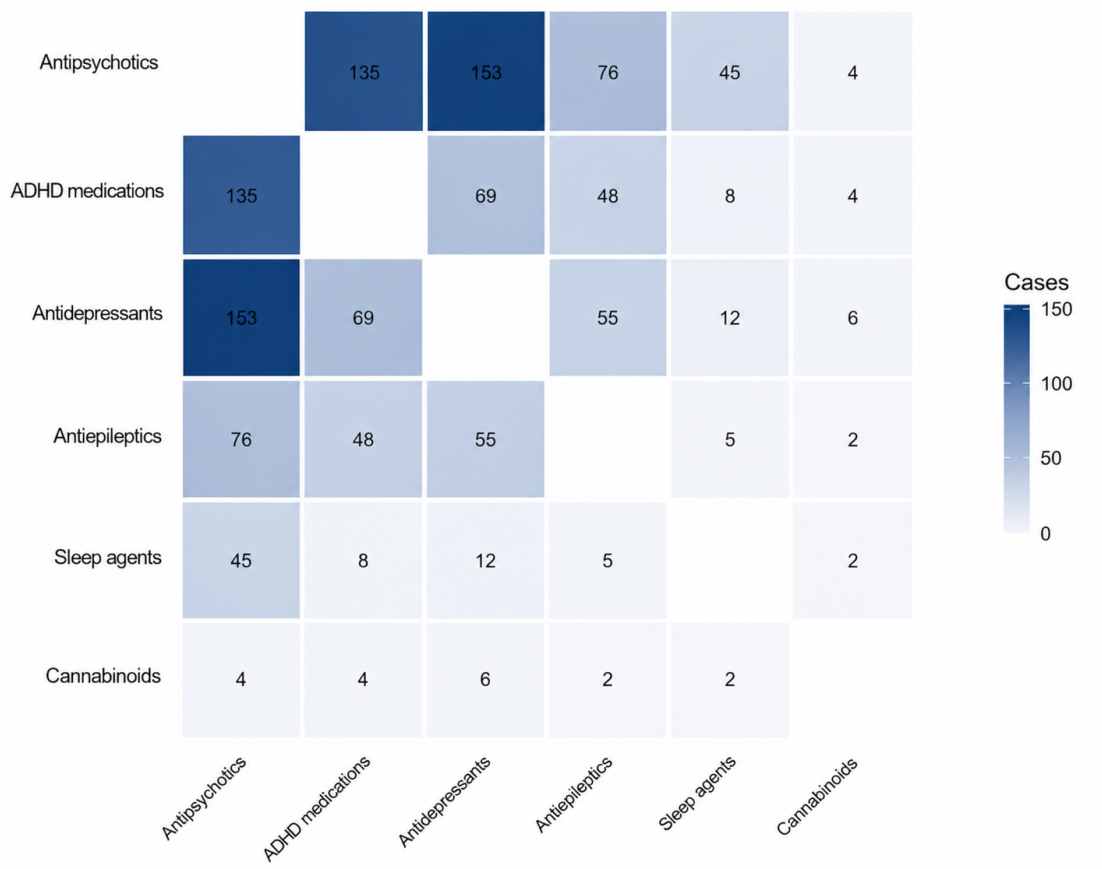


Figure 3c. Polypharmacy burden among pediatric autism-related EudraVigilance reports. (2021-2025)

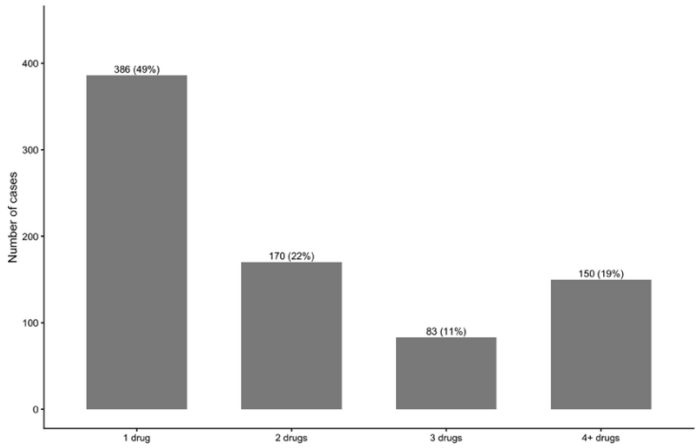
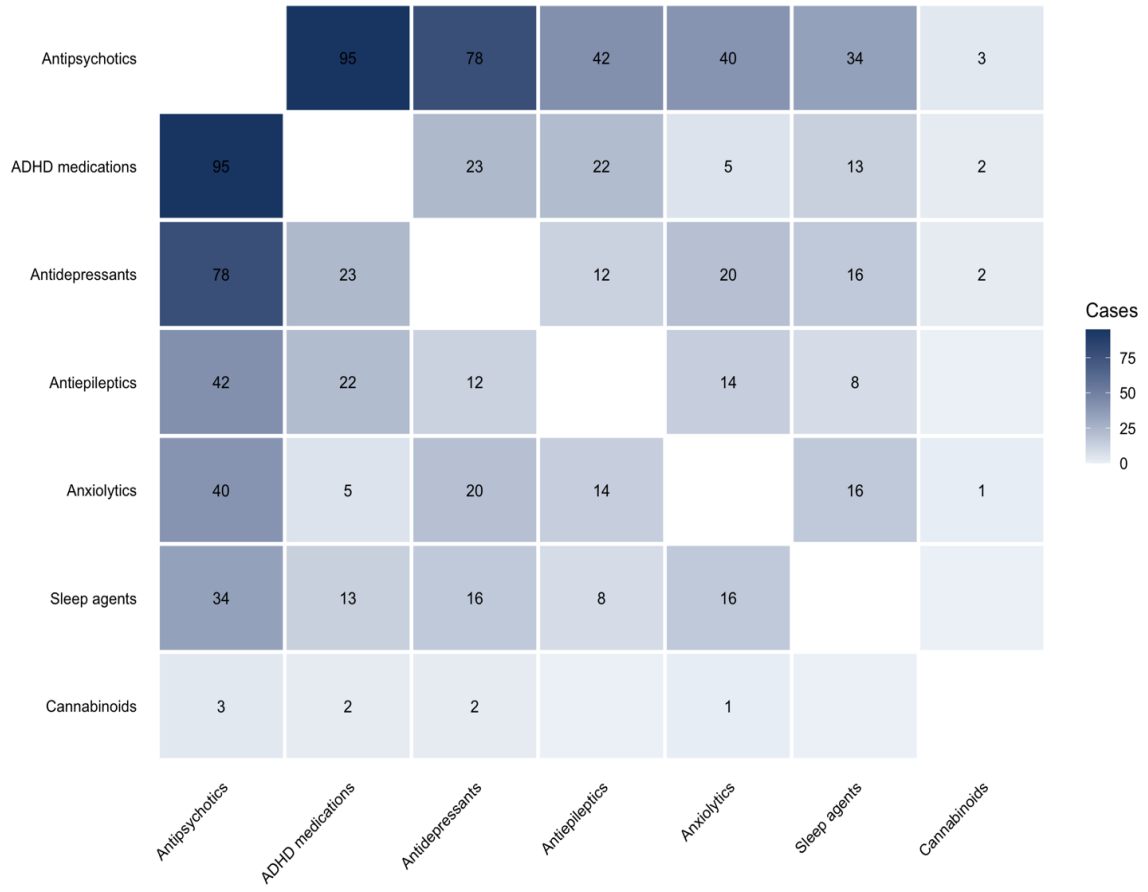


Figure 3d. Heatmap of co-reported medication classes in pediatric autism-related EudraVigilance reports. (2021-2025)



Adverse event profiles

Across both databases, several adverse event categories were repeatedly reported across multiple medication classes, including prolactin-related events, weight-related problems, extrapyramidal symptoms, mood-related symptoms, aggression, agitation, gastrointestinal symptoms, and somnolence (Tables 3 and 4). Supplementary Table 1 summarizes reporting odds ratios (RORs) for selected adverse event categories and supports the descriptive reporting patterns observed across drug classes.

Among antipsychotic-associated reports, prolactin-related events and weight-related problems were the most frequently reported categories in both FAERS (41% and 36%, respectively) and EudraVigilance (30% and 29%, respectively). Mood-related symptoms and extrapyramidal symptoms were also commonly reported across both systems. Reports involving ADHD medications frequently showed in weight-related problems, aggression, prolactin-related events, extrapyramidal symptoms, agitation, irritability, insomnia, and somnolence. Reports involving SSRIs also were by neuropsychiatric adverse events, including aggression, extrapyramidal symptoms, agitation, mood-related symptoms, gastrointestinal symptoms, and

suicidal ideation.

For anti-anxiety medications, extrapyramidal symptoms and prolactin-related events were the most common adverse event categories in both databases. The characteristics of adverse events related to antiepileptic drugs differed significantly between the two databases; the FAERS database more frequently involved weight-related and behavioural adverse events, while the EudraVigilance database more frequently involved anxiety, psychomotor retardation, hypotonia, cognitive impairment, and fatigue. In reports on sleep medications, gastrointestinal symptoms, extrapyramidal symptoms, aggression, restlessness, fatigue, irritability, and cyanosis were found in both databases.

Cannabinoid-related reports were limited. In the FAERS database, the most frequently reported adverse events included agitation, insomnia, psychomotor hyperactivity, extrapyramidal symptoms, and mydriasis. Disproportionality analyses demonstrated expected safety signals for several commonly reported adverse event categories, for example prolactin-related events with risperidone, extrapyramidal symptoms with aripiprazole, aggression with methylphenidate, and suicidal ideation with sertraline (Supplementary Table 1). Due to the limited number of cannabinoid-associated reports, findings related to cannabinoids should be interpreted with caution.

Table 3. Most frequently reported adverse events by drug class in FAERS cases involving children with autism (2020–2025).

Drug class	**Representative drugs**	**Adverse event**	**Cases, n (% within class)**
Antipsychotics (n=822)	Risperidone; Aripiprazole	Prolactin-related events	334 (41%)
		Weight-related problems	296 (36%)
		Mood-related symptoms	217 (26%)
		Extrapyramidal symptoms	135 (16%)
		Aggression	88 (11%)
		Gastrointestinal symptoms	75 (9%)
		Somnolence	68 (8%)
		Increased appetite	55 (7%)
		Agitation	42 (5%)
		Irritability	24 (3%)
		Suicidal ideation	23 (3%)
ADHD medications (n=231)	Methylphenidate; Clonidine	Weight-related problems	64 (28%)
		Prolactin-related events	52 (23%)

		Aggression	41 (18%)
		Extrapyramidal symptoms	23 (10%)
		Agitation	15 (6%)
		Mood-related symptoms	15 (6%)
		Somnolence	14 (6%)
		Irritability	12 (5%)
		Anxiety	9 (4%)
		Insomnia	9 (4%)
Antidepressants (SSRIs) (n=178)	Sertraline; Fluoxetine	Prolactin-related events	66 (37%)
		Weight-related problems	59 (33%)
		Aggression	50 (28%)
		Extrapyramidal symptoms	42 (24%)
		Agitation	28 (16%)
		Mood-related symptoms	28 (16%)
		Gastrointestinal symptoms	21 (12%)
		Suicidal ideation	18 (10%)
		Fatigue	14 (8%)
		Dizziness	13 (7%)
		Hypersexuality	13 (7%)
		Irritability	13 (7%)
		Anxiety	12 (7%)
Anxiolytics (n=69)	Lorazepam; Clonazepam	Extrapyramidal symptoms	17 (25%)
		Prolactin-related events	15 (22%)
		Agitation	8 (12%)
		Suicidal ideation	8 (12%)
		Gastrointestinal symptoms	6 (9%)
		Aggression	5 (7%)
		Increased appetite	5 (7%)
		Weight-related problems	5 (7%)
		Mood-related symptoms	3 (4%)
Antiepileptics (n=108)	Lamotrigine; Valproate	Weight-related problems	51 (47%)
		Aggression	43 (40%)
		Prolactin-related events	42 (39%)
		Extrapyramidal symptoms	14 (13%)
		Pneumonia	12 (11%)
		Agitation	6 (6%)
		Gastrointestinal symptoms	6 (6%)

		Neurotoxicity	5 (5%)
		Decreased appetite	4 (4%)
		Mood-related symptoms	4 (4%)
Sleep agents (n=46)	Melatonin	Cardiac-related events	17 (37%)
		Cyanosis	12 (26%)
		Extrapyramidal symptoms	10 (22%)
		Gastrointestinal symptoms	10 (22%)
		Prolactin-related events	8 (17%)
		Weight-related problems	6 (13%)
		Lethargy	3 (7%)
Cannabinoids (n=8)	Cannabidiol (CBD)	Agitation	6 (75%)
		Insomnia	6 (75%)
		Psychomotor hyperactivity	5 (62%)
		Extrapyramidal symptoms	4 (50%)
		Mydriasis	4 (50%)
		Screaming	3 (38%)
		Fall	1 (12%)
		Gastrointestinal symptoms	1 (12%)

Footnotes: Data were extracted from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) between 2020 and 2025 and restricted to reports involving individuals aged <18 years with autism. Percentages represent the proportion of reports within each drug class. A single report may include multiple adverse events and multiple drug classes.

Table 4. Most frequently reported adverse events by drug class among children with autism cases in the EudraVigilance database (2021–2025)

Drug class	**Representative drugs**	**Adverse event**	**Cases, n (% within class)**
Antipsychotics (n=472)	Risperidone; Aripiprazole	Prolactin-related events	140 (30%)
		Weight-related problems	139 (29%)
		Mood-related symptoms	91 (19%)
		Extrapyramidal symptoms	87 (18%)
		Somnolence	48 (10%)
		Aggression	35 (7%)
		Gastrointestinal symptoms	29 (6%)
		Increased appetite	17 (4%)
		Agitation	17 (4%)
		Increased appetite	17 (4%)

		Fatigue	14 (3%)
		Insomnia	14 (3%)
ADHD medications (n=159)	Methylphenidate; Clonidine	Weight-related problems	25 (16%)
		Decreased appetite	15 (9%)
		Aggression	14 (9%)
		Extrapyramidal symptoms	12 (8%)
		Agitation	11 (7%)
		Irritability	11 (7%)
		Somnolence	11 (7%)
		Insomnia	10 (6%)
		Mood-related symptoms	9 (6%)
		Prolactin-related events	9 (6%)
Antidepressants (SSRIs) (n=72)	Sertraline; Fluoxetine	Extrapyramidal symptoms	17 (24%)
		Aggression	13 (18%)
		Prolactin-related events	12 (17%)
		Mood-related symptoms	10 (14%)
		Weight-related problems	10 (14%)
		Agitation	7 (10%)
		Anxiety	7 (10%)
		Gastrointestinal symptoms	6 (8%)
		Suicidal ideation	6 (8%)
		Irritability	5 (7%)
Anxiolytics (n=25)	Lorazepam; Clonazepam	Prolactin-related events	9 (36%)
		Extrapyramidal symptoms	4 (16%)
		Aggression	3 (12%)
		Somnolence	3 (12%)
		Agitation	1 (4%)
		Diplopia	1 (4%)
		Dizziness	1 (4%)
		Fatigue	1 (4%)
		Gastrointestinal symptoms	1 (4%)
		Mood-related symptoms	1 (4%)
Antiepileptics (n=166)	Lamotrigine; Valproate	Ear disorder	64 (39%)
		Anxiety	53 (32%)
		Psychomotor Retardation	52 (31%)
		Hypotonia	46 (28%)

		Cognitive Disorder	43 (26%)
		Fatigue	42 (25%)
		Aggression	34 (20%)
		Enuresis	33 (20%)
		Oropharyngeal discomfort	33 (20%)
		Extrapyramidal symptoms	29 (17%)
Sleep agents (n=34)	Melatonin	Aggression	11 (32%)
		Gastrointestinal symptoms	5 (15%)
		Agitation	4 (12%)
		Fatigue	4 (12%)
		Extrapyramidal symptoms	4 (12%)
		Irritability	4 (12%)
		Mood-related symptoms	3 (9%)
		Prolactin-related events	3 (9%)
		Screaming	3 (9%)
		Cyanosis	2 (6%)

Footnote: Data were extracted from EudraVigilance between 2021-2025. The values represent the number and percentage of independent cases reporting each adverse event for each class of drugs, with each event counted only once per case.

Serious outcomes in FAERS

Serious outcomes were common across medication classes in FAERS (Table 5). Hospitalization was most frequently reported among anxiolytic/sedative-associated reports (80%), followed by sleep agents (41%), SSRIs (38%), and antiepileptics (33%). Life-threatening outcomes were most frequently reported among antiepileptic-associated reports (19%). Death was uncommon and was reported only in antipsychotic-associated and SSRI-associated reports. Cannabinoid-associated reports were limited, with one hospitalization-associated report identified.

Table 5. Distribution of serious adverse events outcomes by drug class in FAERS reports involving children with autism (2020–2025).

Drug class	**Number of Serious, Adverse Events n (%)**	**Death, n (%)**	**Life-threatening, n (%)**	**Hospitalization, n (%)**	**Disability, n (%)**	**Congenital anomaly, n (%)**	**Required intervention, n (%)**	**Other serious, n (%)**
Antipsychotics (n=822)	547 (67%)	3 (0%)	22 (3%)	193 (23%)	29 (4%)	0	4 (0%)	421 (51%)

Antidepressants (n=178)	168 (94%)	3 (2%)	4 (2%)	67 (38%)	25 (14%)	0	0	133 (75%)
ADHD medications (n=231)	175 (76%)	0	3 (1%)	36 (16%)	2 (1%)	0	0	157 (68%)
Anxiolytics (n=69)	67 (97%)	0	6 (9%)	55 (80%)	5 (7%)	0	0	33 (48%)
Antiepileptics (n=108)	103 (95%)	0	20 (19%)	36 (33%)	1 (1%)	1 (1%)	0	85 (79%)
Sleep agents (n=46)	46 (100%)	0	0	19 (41%)	0	0	0	29 (63%)
Cannabinoids (n=8)	7 (88%)	0	0	1 (12%)	0	0	0	6 (75%)

Footnote: Percentages represent the proportion of reports within each drug class. A single case may contribute to more than one drug class due to concomitant drug use. Serious outcomes were defined based on FAERS outcome codes and included death, life-threatening events, hospitalization, disability, congenital anomaly, required intervention, and other serious medical events. Cases without recorded outcome codes were treated as having no reported serious outcomes.

4.5 Discussion

This study analyzed adverse event reporting patterns related to commonly used medications in children with autism across the FAERS and EudraVigilance databases. Antipsychotics were the most frequently reported medication category, and polypharmacy was prevalent. Recurring reported event categories included prolactin-related events, weight-related problems, extrapyramidal symptoms, behavioural symptoms, gastrointestinal symptoms, and drowsiness. Although reports of cannabinoid-related events were limited, neuropsychiatric adverse event categories were found in these cases.

Many of the observed reporting patterns were compatible with the established safety profiles of psychotropic medications used in pediatric populations. Reports involving antipsychotics commonly included prolactin-related events, extrapyramidal symptoms, weight changes, and somnolence. These patterns are pharmacologically plausible given the dopaminergic, histaminergic, serotonergic, and metabolic effects of second-generation antipsychotics, particularly risperidone.[11–15] Neuropsychiatric adverse events are also common with antidepressants, ADHD medications, anxiolytics, and cannabinoids.[16,17] Antidepressants may cause agitation, aggression, fatigue, mood-related symptoms, or suicidal ideation through serotonergic effects.[18–21] For example, aggression and agitation were frequently recorded among the reports involving sertraline in this study. Reports involving stimulants and α2-adrenergic receptor agonists included weight or appetite changes, irritability, and somnolence.[22,23] These

observations are consistent with known medication effects, but the spontaneous-reporting data cannot establish that the reported medication caused a specific event.[24–26]

Some findings warrant more focused investigation. Ear disorders were among the most frequently reported categories in antiepileptic medication cases, particularly in EudraVigilance. Previous studies have proposed that long-term antiepileptic exposure may contribute to auditory or vestibular toxicity through delayed conduction within auditory pathways.[27] Other cases with antiepileptics show a pattern of adverse neurological events, including hypotonia, psychomotor retardation, cognitive impairment, fatigue, and behavioural symptoms. This may be related to inhibiting the excitability of neurons throughout the central nervous system to prevent seizures.[28,29] Drowsiness and fatigue observed after melatonin supplementation are primarily related to its role as a potent regulator of the sleep-wake cycle.[31,32]

Furthermore, several adverse event categories identified in this study are rarely mentioned in the literature on autism medication strategies. Pneumonia, cyanosis, screaming, and cardiac-related events were also found in specific drug categories. These findings may reflect central nervous system depression, underlying neurological comorbidities, multiple drug exposure, or difficulty in distinguishing drug-related behavioural deterioration from baseline autism-related behaviors. These less-discussed events illustrate the ability of pharmacovigilance databases to identify unusual reporting patterns that may not be apparent in controlled trials or small observational studies. However, they should be considered as potential adverse events rather than established medication-related safety signals.

Serious outcomes were recorded in several medication categories. Their presence highlights the clinical complexity of children represented in pharmacovigilance databases and supports careful monitoring when psychotropic medications are prescribed. However, FAERS and EudraVigilance depend on spontaneous reports, and serious or unusual events may be more likely to be submitted. Therefore, the proportion of reports classified as serious should not be interpreted as the incidence of serious harm. Caution should be exercised when interpreting reported adverse events for different drug classes, especially when a small number of reports were received for a particular class.

Cannabinoid-associated reports were limited, making detailed safety interpretation difficult. The small number of reports should not be interpreted as evidence of a lower adverse-event risk. It may reflect lower levels of cannabinoid exposure in this population or underreporting. Neuropsychiatric adverse events were represented among the identified cannabinoid-associated reports and overlapped with those reported for commonly used psychotropic medications. The available data were insufficient to characterize cannabinoid-related safety signals or permit comparison with established medication classes. Nevertheless, cannabinoids may affect multiple signaling pathways and CYP450-mediated metabolism, potentially influencing the co-

administration of psychotropic drugs.[33–35] This pharmacological possibility supports careful monitoring in future studies, although the present analysis did not directly evaluate cannabinoid-drug interactions.

Polypharmacy is particularly relevant to the interpretation of these findings. Children with autism often received multiple psychotropic medications simultaneously to control co-symptoms, including ADHD, anxiety, sleep disorders, mood disorders, epilepsy, and other comorbidities.[36,37] Certain drug classes exhibited adverse event types that are not typically considered adverse reactions when used alone. For example, extrapyramidal symptoms are not typically expected with ADHD medications or SSRIs when these medications are used alone.[8,38] Their occurrence in these reports may reflect concomitant antipsychotic use.[8] Similarly, prolactin-related events, usually associated with antipsychotics, also occurred across multiple drug classes.[39] These findings suggest that adverse events observed in real-world autism care may reflect overlapping drug effects and psychotropic polypharmacy.

Potential pharmacokinetic and pharmacodynamic interactions may further complicate tolerability. Many psychotropic medications commonly used in autism care affect similar neuropsychiatric pathways and may contribute to shared adverse event profiles.[40] For example, antipsychotics and antidepressant medications can cause agitation and gastrointestinal problems.[41–44] Irritability and somnolence may be reported with both antipsychotics and ADHD medications, whereas extrapyramidal symptoms are more strongly associated with antipsychotic exposure.[8,45–47] In some cases, these adverse reactions may also reflect changes in drug exposure due to concomitant medication.[48] Fluoxetine and sertraline may inhibit CYP2D6-mediated metabolism of antipsychotics, such as risperidone and aripiprazole, potentially exacerbating extrapyramidal symptoms.[49–52] This provides a plausible explanation for some co-reported events, but the present analysis did not directly test drug-drug interactions. The findings therefore support further investigation of medication combinations rather than confirming that a particular interaction occurred.

Differences were observed between the FAERS database and the EudraVigilance database. Reports related to antiepileptic drugs in the EudraVigilance database more frequently involve hypotonia, cognitive impairment, fatigue, and metabolic adverse events, while reports in the FAERS database more frequently involve anxiety, psychomotor retardation, and behavioural disorders. These differences may reflect variations in prescribing habits, reporting behaviors, or potential patient populations across different regions. Meanwhile, similar major neuropsychiatric and metabolic adverse event categories exist in both databases, enhancing the overall consistency of the observed reporting patterns.

In conclusion, this study provides a real-world overview of a real-world overview of medication-related adverse events reporting patterns in children with autism. The findings not only describe the adverse event reporting patterns of commonly used medications but also

highlight the complexity of the combined use of multiple medications in the management of autism. In autism care, overlapping drug effects, multiple drug exposures, and potential drug interactions can all significantly influence the occurrence and tolerability of adverse events. Although cannabinoid-associated reports were limited and insufficient for a comprehensive safety assessment, they provide preliminary information for future monitoring of cannabinoid-related adverse events and drug-drug interactions. These findings can help guide future safety monitoring strategies, provide insights for interpreting adverse events in clinical practice, and support the design of future clinical trials involving cannabinoids and other emerging therapies for children with autism.

4.6 Limitation

This study used two large pharmacovigilance databases, enabling a comparison of adverse event reporting patterns in two major real-world pharmacovigilance systems. Categorizing medications by clinical relevance classes better reflected real-world medication use patterns in children with autism.

However, this study also has some limitations. Spontaneous reporting databases are prone to incomplete data, reporting bias, underreporting, and inconsistent reporting quality. The occurrence of specific drugs and adverse events in reports does not establish a causal relationship, and frequencies derived from spontaneous reports do not represent incidence or relative risk. The lack of a reliable exposure denominator in spontaneous reporting systems limits direct comparisons of adverse event frequencies across different drug categories. Some adverse events may reflect underlying symptoms, comorbidities, or therapeutic indications. The interpretation of drug-specific adverse event patterns can also be complicated by polypharmacy, as many cases involve multiple concomitant medications. Differences between FAERS and EudraVigilance may also reflect differences in reporting practices, queried substances, and regional prescribing patterns.

The disproportionality analysis was limited to FAERS data and did not adjust for potential confounding by indication. In addition, crude ROR estimates may be unstable when based on small numbers of reports, which affected several drug adverse event pairs in this analysis. At the same time, reports related to cannabinoids remain limited, restricting the interpretation of cannabinoid-related safety patterns in children with autism.

4.7 Conclusion

In both pharmacovigilance databases, similar adverse event patterns were observed. However, adverse event characteristics frequently overlapped across different classes of medications used in children with autism, particularly in neuropsychiatric, metabolic, and neurological adverse events. In this population, co-administration of multiple medications can complicate adverse event attribution, tolerability assessment, and clinical monitoring. Reports

related to cannabinoids remain limited, thereby hindering a reliable description of cannabinoid-related safety profiles. These findings show the importance of careful safety monitoring and consideration of concomitant medication use and polypharmacy when evaluating medication use in children with autism.

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Supplementary table 1. Reporting odds ratios for selected grouped adverse event categories associated with commonly used medications in the FAERS database (2020–2025)

Drug	Grouped AE category	ROR (95% CI)	n
Aripiprazole	Extrapyramidal	16.991 (16.16 - 17.864)	1779
	Aggression	11.434 (10.062 - 12.992)	246
	Prolactin-related	10.963 (9.663 - 12.438)	253
	Suicidal ideation	8.219 (7.445 - 9.074)	411
	Agitation	8.169 (7.23 - 9.228)	268
	Increased appetite	7.988 (6.597 - 9.671)	108
	Irritability	7.024 (6.078 - 8.118)	189
	Mood related	4.697 (4.198 - 5.256)	314
	Somnolence	3.676 (3.344 - 4.041)	444
	Weight related	3.619 (2.941 - 4.454)	91
Risperidone	Prolactin-related	711.589 (678.072 - 746.763)	4632
	Weight related	33.052 (30.455 - 35.871)	673
	Increased appetite	22.634 (20.041 - 25.563)	279
	Extrapyramidal	10.913 (10.269 - 11.597)	1150
	Aggression	9.714 (8.438 - 11.183)	201
	Somnolence	5.405 (4.983 - 5.863)	613
	Agitation	5.002 (4.274 - 5.854)	159
	Suicidal ideation	3.592 (3.094 - 4.17)	176
	Irritability	2.868 (2.284 - 3.602)	75
	Mood related	1.658 (1.372 - 2.005)	108
Clonidine	Aggression	9.616 (6.477 - 14.276)	25
	Agitation	6.602 (4.481 - 9.725)	26
	Somnolence	6.579 (5.334 - 8.113)	92
	Prolactin-related	5.05 (2.86 - 8.916)	12
	Weight related	4.301 (3.137 - 5.897)	39
	Irritability	3.402 (1.88 - 6.155)	11
	Insomnia	1.757 (1.225 - 2.521)	33

	Extrapyramidal	1.55 (1.018 - 2.36)	22
Methylphenidate	Aggression	17.036 (14.661 - 19.796)	178
	Irritability	13.047 (11.189 - 15.213)	169
	Agitation	9.036 (7.66 - 10.659)	145
	Mood related	5.507 (4.747 - 6.39)	179
	Insomnia	3.752 (3.314 - 4.247)	259
	Extrapyramidal	3.257 (2.818 - 3.765)	188
	Somnolence	2.504 (2.129 - 2.946)	149
	Prolactin-related	1.138 (0.66 - 1.962)	13
Quetiapine	Agitation	12.744 (11.494 - 14.13)	381
	Aggression	9.223 (7.968 - 10.675)	186
	Extrapyramidal	8.912 (8.335 - 9.53)	930
	Prolactin-related	6.605 (5.545 - 7.867)	129
	Mood related	3.68 (3.229 - 4.195)	230
	Weight related	3.282 (2.421 - 4.448)	42
	Neurotoxicity	1.562 (1.028 - 2.375)	22
Sertraline	Suicidal ideation	10.973 (9.953 - 12.099)	426
	Agitation	7.891 (6.864 - 9.072)	204
	Extrapyramidal	6.503 (5.983 - 7.068)	587
	Aggression	5.962 (4.905 - 7.246)	103
	Irritability	4.541 (3.715 - 5.551)	97
	Weight related	4.17 (3.108 - 5.595)	45
	Mood related	4.059 (3.544 - 4.649)	214
	Anxiety	3.747 (3.429 - 4.093)	515
	Prolactin-related	2.804 (2.104 - 3.737)	47
	Dizziness	2.049 (1.867 - 2.248)	465
	Gastrointestinal symptoms	1.615 (1.525 - 1.712)	1279
	Hypersexuality	1.227 (0.172 - 8.732)	1
Cannabidiol (CBD)	Psychomotor hyperactivity	7.028 (4.93 - 10.019)	31
	Screaming	5.845 (3.135 - 10.899)	10
	Agitation	3.442 (2.715 - 4.364)	69
	Insomnia	1.465 (1.23 - 1.746)	127
	Fall	1.193 (1.011 - 1.408)	143
	Gastrointestinal symptoms	1.179 (1.096 - 1.269)	775

Supplementary table 2. Drug name standardization and medication class assignment used in FAERS analyses

Medication Class	**Standardized Drug**	**Brand Names / Alternative Names**

		Merged
Antipsychotics	Risperidone	Risperdal, Risperdal Consta, Risperdal M Tab
	Aripiprazole	Abilify, Abilify Maintena
	Paliperidone	Invega
	Quetiapine	Seroquel
	Olanzapine	Zyprexa
	Clozapine	Clozaril
	Ziprasidone	Geodon
	Lurasidone	Latuda
	Haloperidol	Haldol
	Chlorpromazine	Thorazine
	Asenapine	Saphris
Antidepressants	Fluoxetine	Prozac
	Sertraline	Zoloft
	Escitalopram	Lexapro
	Citalopram	Celexa
	Fluvoxamine	Luvox
	Paroxetine	Paxil
	Venlafaxine	Effexor
	Desvenlafaxine	Pristiq
	Duloxetine	Cymbalta
	Bupropion	Wellbutrin
	Mirtazapine	Remeron
	Trazodone	Desyrel, Oleptro
	Amitriptyline	Elavil
	Nortriptyline	Pamelor
	Clomipramine	Anafranil
Sleep Agents	Melatonin	—
	Zolpidem	Ambien
	Eszopiclone	Lunesta
	Zaleplon	Sonata
ADHD	Methylphenidate	Ritalin, Concerta, Daytrana, Focalin
	Dexmethylphenidate	—
	Amphetamine	Adderall, Dexedrine
	Lisdexamfetamine	Vyvanse
	Atomoxetine	Strattera
	Guanfacine	Intuniv, Tenex
	Clonidine	Kapvay

Anxiolytics	Lorazepam	Ativan
	Diazepam	Valium
	Clonazepam	Klonopin
	Alprazolam	Xanax
	Buspirone	Buspar
	Hydroxyzine	Atarax, Vistaril
Antiepileptics	Valproate	Valproic acid, Divalproex, Depakote
	Lamotrigine	Lamictal
	Levetiracetam	Keppra
	Topiramate	Topamax
	Oxcarbazepine	Trileptal
	Gabapentin	Neurontin
	Zonisamide	Zonegran
	Phenobarbital	Luminal
	Phenytoin	Dilantin
Cannabinoids	Cannabidiol	CBD, Epidiolex, Epidyolex
	THC / Dronabinol	THC, Tetrahydrocannabinol, Dronabinol
	Nabilone	Cesamet
	Nabiximols	Sativex
	Cannabis	Marijuana

Chapter 5: Discussion

5.1 Data summary and integration of findings

This thesis uses a triangulation approach to examine the current situation of medical cannabis use in children with autism and explores factors that need to be considered in future pediatric clinical trials in Canada. Together, the findings identify the gaps between family interest in cannabinoids and the evidence available to support their use.

The literature review indicates possible improvements in associated symptoms, particularly irritability, sleep disturbance, and anxiety.[1–6] However, these findings were reported more consistently in observational studies than in randomized controlled trials. The randomized controlled trials generally did not demonstrate consistent benefits on prespecified primary outcomes, although selected secondary outcomes suggested possible symptom-specific effects.[2,4–7] Differences in cannabinoid formulations and outcome measures further limited comparison across studies.[7–9] Small sample sizes and short follow-up periods further prevent firm conclusions about long-term efficacy and safety.[10,11]

This national survey demonstrated that developmental pediatricians frequently receive inquiries from families regarding the use of medical cannabis in children with autism. Despite growing clinical interest, most participants reported limited formal training and access to evidence-based pediatric guidance related to cannabinoid use. Uncertainty regarding dosing strategies, adverse effects, product quality, and potential drug interactions were commonly identified as major barriers to clinical discussions. However, many respondents also expressed willingness to discuss future clinical trials with eligible patients. These findings highlight the need for physician education and pediatric-specific clinical resources to support evidence-based discussions with families and future research participation.

The pharmacovigilance analysis explored the challenges of interpreting adverse events in children with autism during pediatric cannabinoid trials. Children with autism often present with multiple comorbidities and receive several psychotropic or neurological medications simultaneously, creating a complex polypharmacy environment.[12,13] Consequently, an adverse event observed during cannabinoid treatment may reflect the study product, a concomitant medication, an underlying condition, or an interaction among these factors. The reporting patterns identified in FAERS and EudraVigilance illustrate this difficulty but cannot establish causality or quantify medication-related risk. Although this approach provides important background safety information, only a small number of cannabinoid-associated reports were identified. This may reflect limited exposure, underreporting, inconsistent product identification, or differences in reporting pathways. The available pharmacovigilance data therefore do not permit comparison of cannabinoid safety with that of established medication classes.

In summary, the three studies indicate a gap between family interest in cannabinoids and the evidence available to guide clinical decisions. The literature review identified preliminary symptom-specific signals but insufficient evidence to guide clinical use. Consistent with this uncertainty, developmental pediatricians reported limited confidence in counselling families about cannabinoid efficacy, dosing, and safety. The pharmacovigilance findings further indicate that the assessment of treatment-emergent events must account for underlying conditions and concomitant medications.

5.2 Knowledge gaps and future directions

Despite developmental pediatricians reporting frequent inquiries from caregivers of children with autism about medical cannabis, significant knowledge gaps remain. The limited number of high-quality randomized controlled trials contributes to uncertainty when physicians counsel families about potential benefits and risks of cannabinoid use in children. Most existing studies are observational and include relatively small sample sizes and short follow-up periods. These limitations may reflect some challenges with funding and conducting prospective, interventional studies. While most observational studies report potential benefits, their findings are vulnerable to selection bias, expectation effects, and the absence of placebo control. The current evidence is insufficient to draw definitive conclusions about efficacy and long-term safety. Future trials should define a specific target before enrolment and select a primary outcome that directly measures that target. Associated symptoms such as irritability, anxiety, or sleep disturbance should be evaluated separately from the core features of autism. This approach would allow a clearer assessment of whether cannabinoids provide a clinically meaningful symptom-specific benefit.

Heterogeneity in cannabinoid exposure also limits interpretation of the existing literature. Published studies evaluated different cannabinoid formulations, dosage regimens, and routes of administration, which further limited comparison across studies. Future clinical trials should use consistent, high-quality cannabinoid products and well-defined protocols. These measures would improve reproducibility and allow findings to be interpreted in relation to a defined cannabinoid product rather than medical cannabis as a single intervention.

The clinical relevance of drug interactions remains unclear, despite being identified as a barrier to cannabinoid use by developmental pediatricians. Children with autism often require multiple medications to treat related behavioural and neurological disorders, creating a complex polypharmacy environment. Cannabinoids, particularly CBD, may affect several drug-metabolizing enzymes and could alter exposure to some concomitant medications. The published literature and pharmacovigilance reports indicate that concomitant medication use is common, but few studies have specifically assessed whether it influences cannabinoid efficacy or adverse events. All concomitant medications should be documented at baseline and monitored

throughout treatment. Where clinically appropriate, medication regimens should remain stable during the intervention period. Potential interactions should be assessed prospectively rather than inferred solely from co-reported adverse events.

Furthermore, long-term safety data in children remain limited. As children are still undergoing neurophysiological development, the long-term effects of cannabinoids require further investigation. Future trials should distinguish pre-existing symptoms from treatment-emergent events and apply standardized definitions when recording adverse events. Extended follow-up and comprehensive safety monitoring are crucial for better understanding delayed adverse events and developmental outcomes. The feasibility of conducting such trials in Canada will also depend on appropriate research infrastructure, physician engagement, and the willingness of families to participate. Filling these knowledge gaps will contribute to improving evidence-based clinical decision-making and to the development of future clinical guidance for children with autism in Canada.

5.3 Overall limitations

This thesis also has limitations that should be considered when interpreting the results. The evidence found in the systematic review exhibits significant heterogeneity in study design, cannabinoid formulations, dosing strategies, outcome measures, and follow-up time. Most existing studies are not randomized clinical trials and have limited sample sizes, which restricts the ability to draw definitive conclusions about efficacy and long-term safety. None of the included studies was conducted in Canada. Differences in healthcare delivery, regulatory requirements, patterns of cannabis access, and available products may therefore limit the direct applicability of the findings to the Canadian context.

The survey of developmental pediatricians may be subject to response bias, as developmental pediatricians who are more interested in or experienced with medical cannabis may be more likely to participate. The response rate was relatively low, and the results may not fully represent the views of all developmental pediatricians in Canada. The survey also relied on self-reported experiences and perspectives, which may be influenced by recall bias. In addition, this project did not directly examine the perspectives of children with autism or their caregivers, despite their central role in treatment decisions and clinical trial participation.

Pharmacovigilance databases have inherent limitations of spontaneous reporting systems, including underreporting, incomplete clinical information, duplicate reporting, and reporting bias. These databases cannot be used to estimate incidence rates or establish causal relationships between medications and adverse events. Polypharmacy further complicates attribution because a single report could include several medications and be assigned to more than one drug class. Differences in database structure, coding conventions, and reporting requirements also limit

direct comparisons between FAERS and EudraVigilance. Due to the limited number of reports related to cannabis use in children with autism, it is impossible to meaningfully describe the safety signals associated with cannabinoids or to compare them with existing drug categories.

Finally, while this thesis employs three complementary research methods to contribute to a more comprehensive understanding of medical cannabis use among children with autism, differences in sources and levels of evidence may limit direct comparisons. These findings are complementary but cannot be combined quantitatively or interpreted as independent confirmation of cannabinoid efficacy or safety. These limitations should be fully considered when interpreting the findings.

5.4 Impact and applications of our findings

The findings have several important implications for clinical care and research. From a clinical perspective, developmental pediatricians frequently receive inquiries from families with children with autism about medical cannabis. However, developmental pediatricians reported limited training and access to pediatric resources to help families of autistic children. Educational materials could help clinicians explain the current evidence and communicate uncertainties regarding dosing and long-term safety. Family-oriented resources could similarly support informed discussions about potential benefits, adverse effects, and the limitations of commercially available products. These resources should provide balanced information for future cannabinoid use.

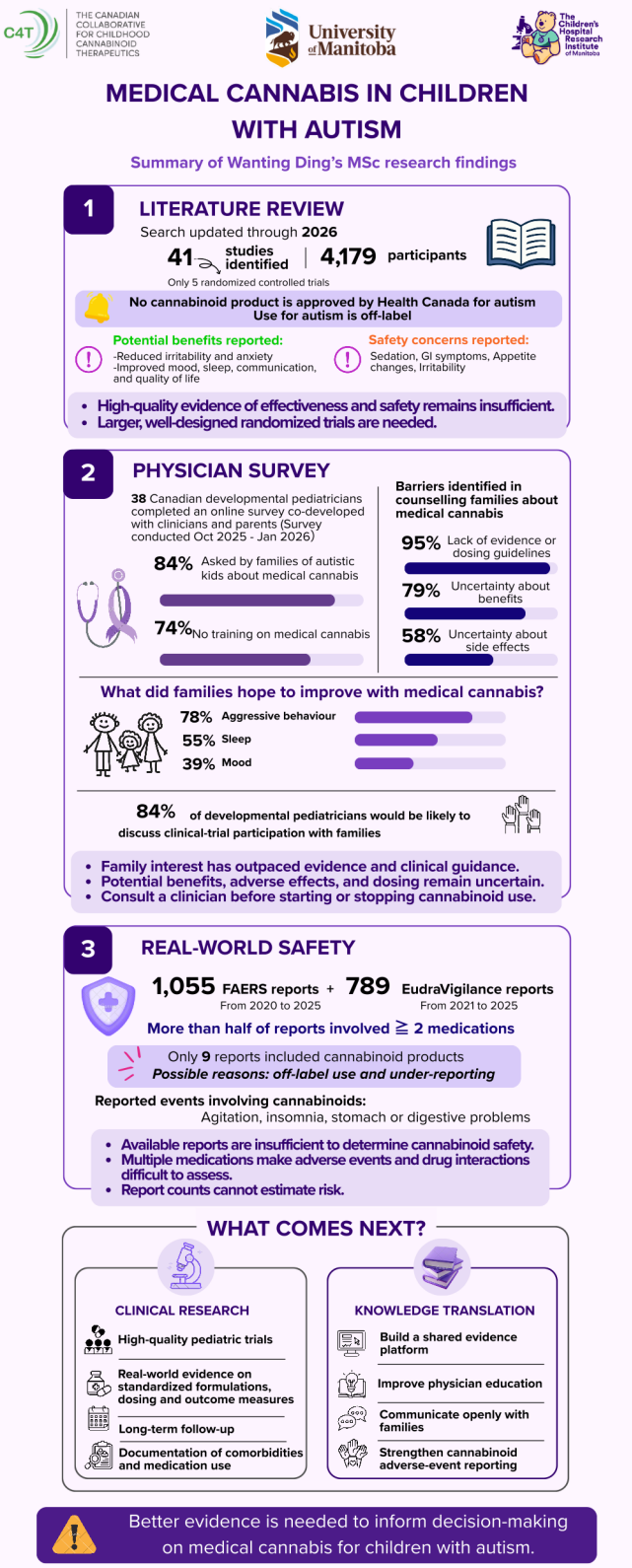
From a research perspective, this thesis emphasizes the importance of methodological rigor in future cannabinoid research. Importantly, developmental pediatricians expressed a willingness to discuss future cannabinoid clinical trials with eligible families. Physician' willingness to discuss clinical trials suggests that pediatricians could contribute to identifying potentially eligible families and providing comprehensive information about research participation. Engagement with children and caregivers will also be important when selecting outcomes and developing acceptable study procedures. Furthermore, the findings emphasize the importance of documenting concomitant medications and considering the complexities of polypharmacy in children with autism.

This thesis also provides practical information for the design of future pediatric cannabinoid clinical trials. The physician concerns identified in the survey help determine priorities for safety monitoring. Meanwhile, pharmacovigilance results provide important contextual information for interpreting adverse events in children with autism. These findings collectively support prospective clinical trials in Canada. Strengthening the evidence base for medical cannabis use in children with autism will help make more informed clinical decisions and promote the development of future evidence-based clinical guidelines in Canada.

5.5 Conclusion

Overall, conducting patient and family-centered pediatric clinical trials of cannabinoids in autism in Canada is essential to bridging the gap between access and evidence. Until clinically meaningful efficacy and acceptable long-term safety are established, cannabinoids should not be considered a standard treatment for autism. The immediate priorities are rigorous clinical research and balanced educational resources that support informed discussions among clinicians, children, and families.

5.6 Infographics summary of study findings to inform future development of educational materials for health care professionals and families



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