SELECTIVE STUDIES ON THE CHALLENGES OF CANNABIS USE IN CHILDREN, YOUTH, AND YOUNG ADULTS

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ABSTRACT

The legalization of medical and recreational cannabis in Canada poses several challenges and opportunities in children, youth, and young adults. A clear understanding of the challenges and opportunities, though, remains elusive as cannabis use in younger people is vastly understudied. An evidence base is growing for use of medical cannabis to treat refractory pediatric seizures and to aid in the management of oncology pain. With some conditions, however, there is no data to support efficacy or safety but public enthusiasm has promoted off-label use. For example, some parents have admitted to administering cannabis for refractory symptom management of their child's attention deficit hyperactivity disorder (ADHD). Presently, there are no trials on the efficacy or safety of medical cannabis in children, youth, or young adults with ADHD. Dosing recommendations for such studies will require an understanding of the pharmacokinetics of cannabis components in children diagnosed with ADHD or other off-label conditions. Children and youth who are successfully stabilized on medical cannabis have also experienced other challenges. For example, some children who take medical cannabis require a dosage during the school day. School policies that address the risks of recreational cannabis can be prohibitive for those who require cannabis to treat a medical condition. With respect to recreational cannabis, its use in youth is concerning since cannabis can cause harm to the developing brain. Education is needed for youth, their parents, and teachers to promote risk reduction and healthy choices.

This PhD program explored both medical and recreational aspects of cannabis use in the vulnerable population of children, youth, and young adults. In the context of medical use, the first objective was to determine treatment efficacy and pharmacokinetics of cannabis in ADHD, a pediatric condition where there was a perceived benefit, but lack of evidence. We designed a proof-of-concept study, but experienced significant delays with the Covid-19 global pandemic and challenges with study recruitment. Nevertheless, we published the study protocol and a case report describing our experience and cannabinoid plasma levels in three young adults taking medical cannabis for treatment of their ADHD.

The potential challenge of medical cannabis at schools was also examined. A scoping review of the scientific literature, Canadian policies and laws underscored the lack of clear guidance on medical cannabis in schools and discrepancies across jurisdictions. Qualitative studies exploring the experiences of clinicians who authorize medical cannabis for school-aged children and caregivers highlighted challenges for these individuals, and guidance for moving this area forward.

To address the use of cannabis in children and youth in a recreational context, we developed an educational toolkit for middle school and high school students, parents, and teachers. This education program was approved as a curriculum resource by the Ministry of Education in Saskatchewan and can be accessed by Saskatchewan teachers. The evolving cannabis legislation in Canada requires effective education and communication, both for reducing the risks associated with recreational cannabis and decreasing the stigma for those who require it medically.

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LIST OF ABBREVIATIONS

ACMPR	Access to Cannabis for Medical Purposes Regulations
ADME	absorption, distribution, metabolism, and excretion
ADHD	attention-deficit/ hyperactivity disorder
ASD	autism spectrum disorder
AUC	area under the plasma-concentration time curve
CanLII	Canadian Legal Information Institute
CBC	cannabichromene
CBD	cannabidiol
CBDA	cannabidiolic acid
CBG	cannabigerol
CBN	cannabinol
CCIC	Canadian Consortium for the Investigation of Cannabinoids
CEER-9	Clinical Evaluation of Emotional Regulation-9
CFAMM	Canadians for Fair Access to Medical Marijuana
CHASR	Canadian Hub for Applied and Social Research
C_{max}	maximum plasma concentration
CPhA	Canadian Pharmacists Association
CPSP	Canadian Paediatric Surveillance Program
CTADS	Canadian Tobacco, Alcohol and Drugs Survey
CYP	cytochrome P450
C4T	Canadian Collaborated for Childhood Therapeutics
DAT	dopaminergic transporter
DIN	Drug Identification Number
DRE	drug resistant epilepsy
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECS	endocannabinoid system
EVALI	e-cigarette or vaping use-associated lung injury
FAAH	fatty acid amide hydrolase
GPR55	G protein-coupled receptor 55

ITT	Intent to Treat
LC–MS/MS	liquid chromatography–tandem mass spectrometry
MAGL	monoacylglycerol lipase
MMAR	Medical Marihuana Access Regulations
MMM	Marijuana Motives Measure
MMPR	Marihuana for Medical Purposes Regulations
NASN	National Academy of School Nurses
NPH	Natural Health Product
ODD	oppositional defiant disorder
PHQ-9	Patient Health Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
PTSD	post traumatic stress disorder
REACH	Real Education About Cannabis and Health program
SCARED	Screen for Child Anxiety Related Emotional Disorders
SHA	Saskatchewan Health Authority
SHINE	School Health Initiative with Nursing Education
Safe SHIP	Safe School Health Improvement Project
SNAP-IV	Swanson, Nolan, and Pelham-IV Questionnaire
THC, Δ^9-THC	delta-9-tetrahydrocannabinol
THCA	tetrahydrocannabinolic acid
THCV	tetrahydrocannabivarin
UGT	UDP-glucuronosyltransferase
2-AG2	2-arachidonoyl glycerol

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CHAPTER 1. INTRODUCTION

Preface

The legalization of medical and recreational cannabis in Canada poses several challenges and opportunities in children, youth, and young adults and this dissertation describes selected studies within this evolving landscape. Opportunities relate to the therapeutic potential of medical cannabis in childhood illnesses where conventional medicines do not provide adequate symptom relief. An evidence base is growing for use of medical cannabis to treat refractory pediatric seizures and to aid in the management of oncology pain. With some conditions, however, there are no studies to support efficacy or safety but significant enthusiasm from the public has promoted off-label use. Public perceptions of cannabis in Canada continue to evolve, and many perceive cannabis to be a safer alternative to traditional medications. With lack of evidence to provide guidance, caregivers and clinicians are placed in a precarious position. Consider a situation where a child has ADHD, for example, but the current medications offer inadequate symptom control. The parent seeks a solution and discovers through the social web and grey literature where parents tout cannabis as being effective for symptom management. The parent inquires further with the child's clinician: Some clinicians show reluctance as there is no evidence; others knowing that the evidence will take time are willing to 'experiment' with their patients given the fundamental role the endocannabinoid system plays on neurological homeostasis.

The clinician is then presented with the challenge of suggesting a dose of cannabis in the absence of evidence. Pharmacokinetic information is necessary for selecting an appropriate dose because it helps predict drug exposure in the individual. This is especially important for children since their body's absorption, distribution, metabolism, and excretion (ADME) processes undergo ontogeny (developmental maturation). As such, exposure levels as governed by the bioavailable dose and systemic clearance may change throughout childhood, possibly necessitating a dosage adjustment as the child gets older. Furthermore, age-related distributional properties might play a role in brain exposure due to developmental changes in the transport properties at the blood-brain-barrier and possible plasma protein binding changes which could affect interpretation of the blood cannabinoid concentrations in pharmacokinetic studies. Before initiating medical cannabis for ADHD symptoms, it would also be ideal for the clinician to have data on its effectiveness. Randomized controlled studies, which provide the best source of evidence for drug efficacy, are time consuming, difficult to undertake and expensive. Observational studies and case reports can provide descriptive data that can be helpful for making treatment decisions in their absence.

Children who take medical cannabis may have dosing regimens that require an adult to administer a dose while in school. This is a concern because not all school policies regarding cannabis are designed to facilitate medical use. Given that some children are using cannabis for legitimate medical purposes, as well as cannabis' easy accessibility since the legalization of recreational cannabis, this creates greater opportunity for children to 'experiment' with cannabis. Recreational cannabis in children, youth and young adults presents a risk to child development, particularly brain development; and there is a need to educate children about cannabis. We know that the most impactful way to educate is when children are involved in the process. There are a multitude of educational strategies, but the constructivist approach seems particularly suited to this context. An educational tool kit co-constructed with youth could be applied provincially to standardize the education around cannabis.

Literature Review

1.1 The Legalization of Cannabis in Canada

Cannabis has been used therapeutically and recreationally for thousands of years across many cultures and was one of the earliest plants cultivated by humans [1]. It was introduced into Western medicine in the 19th century, and was used as a sedative-hypnotic or analgesic, or to improve appetite and digestion, in addition to other purposes [2]. Its use as a medicine diminished at the turn of the decade, largely due to the difficulties in obtaining consistent results with varying batches [1]. However, as medical use of cannabis began to fall out of practice, recreational use became more popular in the United States [3]. The extent to which cannabis was used for psychoactive purposes in Canada in the early 1900's, though, is unknown [3]. In 1923, cannabis was added to the list of prohibitive drugs under Canadian law along with opium, heroin, and cocaine [2,5]. Cannabis accounted for only 2% of Canadian drug arrests between 1941 and 1961 [4]. It was not until the late 1960's that recreational use of cannabis in Canada began to flourish, particularly amongst the younger generations [3]. Renewed interest in medical cannabis intensified as the chemical composition became characterized, as evidenced by the increasing number of scientific publications from 1965 and onward [1]. Although cannabis remained illegal, public support for both medical and recreational cannabis in Canada continued to increase over the latter part of the 20th century [1,3].

In 2001, a major change in legislation occurred that eased restrictions on cannabis in Canada. The inception of the 'Medical Marihuana Access Regulations' (MMAR) program allowed patients to obtain cannabis for specific severe/chronic medical conditions that were federally sanctioned [6]. Under this model, the patient had to register as an authorized medical cannabis user and receive authorization from a physician, which enabled the patient to obtain medical cannabis from Health Canada directly, grow it, or rely on a designated supplier to grow it on their behalf [6]. Uptake of medical cannabis was extremely limited with this model largely due to the program's selectiveness, and many patients who used medical cannabis continued to source it outside of the program [6,7]. Over the next several years, the MMAR underwent several modifications and medical cannabis was no longer limited to patients experiencing specific conditions. The

Marihuana for Medical Purposes Regulations (MMPR) replaced the MMAR in 2013, whereby individuals with a medical need could access quality-controlled dried product as a commercial product from an authorized producer [8]. In 2016, the Access to Cannabis for Medical Purposes Regulations (ACMPR) was instated in response to a court decision that restricting legal access to only dried cannabis from a licensed producer was unconstitutional [8]. The ACMPR allowed patients who had the authorization of their health care practitioner to access cannabis either by a) registering with a licensed producer; or b) registering with Health Canada to grow a limited amount on their own; or c) designating someone else to produce it on their behalf [8].

The *Cannabis Act* (also known as Bill C-45) was instated in October 2018 making Canada the second country in the world to legalize and regulate cannabis for recreational use at the federal level [9-11]. In addition to medical access [12], this legislation now enables adults in Canada to purchase, possess, consume, and grow a limited amount of cannabis for recreational use [9]. The purpose of the act was to redirect governmental focus and resources from criminal prohibition to regulation, with the downstream outcomes of taking a risk reduction approach to the illicit market, reducing the burden on the justice system, promoting a safety and quality regulatory framework for cannabis consumption, and restricting youth access [10,11]. The *Cannabis Act* is subject to provincial or territorial restrictions, which further govern cannabis use in Canada.

1.2 Cannabis in Children, Youth and Young Adults

Medical Cannabis

The interest in medical cannabis has increased dramatically over the past several years. Patients with various medical conditions are taking cannabis with or without health care provider directives or are asking for information about it [13]. Purported benefits, including relief from variety of symptoms, have been promoted by advocacy groups and the media. Coupling this with increased accessibility from the recent changes in federal legislation, it is unlikely that the interest in cannabis use will change. Research in this area, however, has not kept pace with public interest. High-quality supporting evidence for the efficacy of medical cannabis is lacking for most conditions [14].

Understanding the impact of medical cannabis is of particular importance in children, youth, and young adults. During the developmental stages an individual may be unpredictably impacted by drug therapy because growth and maturation complicate drug dosing and clinical responses to therapy [15,16]. Although pediatric doses of medications are often extrapolated from adult studies, important physiologic differences exist between children and adults. Pharmacodynamic and pharmacokinetic processes of absorption, distribution, metabolism, and excretion undergo changes with growth and development which make this population unique. Children can experience different growth and developmental trajectories adding another layer of unpredictability within this heterogenous population [15]. Absorption is affected by changes in gastric pH, for example, which is neutral within the first 10 days of life, and declines to adult levels by about 2 years of age [15-17]. Volume of distribution changes dramatically during growth as it is influenced by body composition, including the ratios of fat, muscle, and intracellular and extracellular water. The highest body water-to-fat ratio is found in neonates and young infants, whereas older infants and toddlers have the highest fat-to-body water ratio, only to mirror adult ratios later in childhood [15,18]. Protein binding is reduced in infants due to decreased concentrations of circulating plasma proteins, such as albumin and α_1-acid glycoprotein. This results in higher distribution of some medications and may necessitate a decrease in dosage [19]. Limited data in neonates suggests that the transport of drugs across the blood-brain barrier may be increased compared to adults [19] and the ontogeny of efflux transporters may influence the activity of some drugs on the brain [16]. Important developmental differences are also seen with drug metabolism: Delayed maturation of the cytochrome P450 (CYP) enzyme system may be responsible for the toxicity of some drugs in the very young. The pattern of enzyme activity evolves over the first few months in neonates and reaches or exceeds adult levels around two years of age [15,19]. The ontogeny of phase II reactions such as glucuronidation is less clear [15]. Elimination pathways of the kidney (glomerular function and tubular secretion) are immature at birth. However, profound anatomical and functional changes occur in toddlers and preschool children, resulting in renal elimination rates that can exceed that of adults before subsequently returning to adult levels [16]. Understanding the nuanced effect that age and development may have on pharmacokinetics is critical information required to design a dosing regimen for a clinical trial with cannabis [16].

Medical cannabis has been used most in younger patients to treat specific types of epilepsy. These tend to be severe forms of the disease, such as Dravet and Lennox-Gastaut syndromes, in which such patients are resistant to standard treatments (e.g., antiepileptics such as valproic acid, ketogenic diet). A recent systematic review and meta-analysis of pure cannabidiol (CBD) and CBD-rich medical cannabis showed that CBD is more effective than placebo in treating resistant epilepsy, regardless of the etiology and dosage ($p < 0.00001$) [20]. Adverse events were more common in the shorter term and favorable in the longer term [20]. Selected prospective trials provide evidence of efficacy in deceasing seizures [21-27] but only a few studies have examined the pharmacokinetic profile of cannabis in a pediatric cohort [28-30]. Given the important impact developmental maturation can have drug processes, an appropriate understanding of CBD pharmacokinetics in the pediatric population is essential [28].

Chemotherapy induced nausea and vomiting has also been successfully treated with cannabis-based medicine in older studies (using Δ^9THC, dronabinol, and nabilone) showing that tetrahydrocannabidiol (THC) is at least as effective than other antiemetics (including prochloperazine, metoclopramide, and domperidone) [31-37]. However, these studies were small in size and there is a lack of data comparing cannabis or cannabinoids to newer antiemetics, such as 5-HT_3 antagonists (e.g., ondansetron, granisetron) or aprepitant.

Other conditions in children, youth and young adults treated with medical cannabis in include autism spectrum disorder (ASD), spasticity, pain, posttraumatic stress disorder (PTSD), and Tourette syndrome, albeit with much less evidence [31,32]. A recent systematic review summarized the literature of cannabis use for ASD and found five studies in children, which used questionnaires, forms, and subjective reports of family members or caregivers to assess changes in symptoms [38]. The studies used varied proportions of CBD and THC and reported improvements in a variety of ASD-related symptoms including self-mutilation and anger bouts, hyperactivity, sleep problems, anxiety, psychomotor agitation, irritability, aggressiveness, sensory sensitivity, cognition, attention, social interaction, language change, depression, and especially restlessness. Of note, none of the studies included cognitive assessment through neuropsychological tests [38]. Dronabinol, a synthetic form of THC, has shown promising effects to treat spasticity in palliative care in an open label uncontrolled retrospective study [39], and may help to relieve neuropathic pain as indicated by a case report of two adolescents [40]. One case report described the effectiveness of cannabidiol oil in improving anxiety and insomnia associated with PTSD in a 10-year-old girl [41]. In a case report with a 16-year-old girl, Δ^9THC decreased tic severity and improved quality of life with treatment-refractory Tourette syndrome [42]. Cannabis has also been adecdotally purported for other conditions in children such as depression, anxiety, ADHD, migraines, anorexia, and arthritis, but there is insufficient evidence to support treatment.

Recreational Cannabis

In contrast to medical cannabis, recreational cannabis involves using cannabis for personal enjoyment rather than for therapeutic benefit. Globally, cannabis is the most used psychoactive substance, with over 180 million people aged 15-64 consuming it for non-medical purposes [43,44]. Cannabis is primarily used to achieve intoxication or a "high", which gives the user a feeling of exhilaration, elevation, or delight [45].
The Marijuana Motives Measure (MMM) outlines five kinds of motives for using cannabis, including enhancement (e.g., "I like the feeling"), social (e.g., "It helps me enjoy the setting"), coping, conformity, and expansion (e.g., "to be open to experiences") [45,46].

Specific populations are particularly susceptible to the potential harms of cannabis. These include pregnant women, those who are still undergoing brain development (i.e., children, youth, and young adults), individuals with low socioeconomic status, or mental illness [47,48]. Long-term frequent cannabis use during brain development in children, youth and young adults may lead to deleterious effects related to attention, memory and learning centers of the brain [49]. Studies have indicated that increased risk of serious mental health conditions, including psychotic symptoms, schizophrenia, and depression, as well as the risk of suicide are associated with the early initiation of cannabis use [50-52]. The risks of cannabis use before the age of 25 may also lead to an increased risk of dependency, driving while intoxicated, and decreased academic performance [54-55]. Over the past several years THC levels have increased in cannabis products and youth who use cannabis regularly are more likely to use other substances [56-58].

Many younger people are using recreational cannabis, which is associated with the aforementioned risks. Compared with other developing countries, cannabis use in youth in Canada has increased, and a higher prevalence is noted in this age group compared to adults [43,59]. The Canadian Tobacco, Alcohol and Drugs Survey (CTADS) is a national survey conducted by Statistics Canada biennially. According to 2017 results, 19% of youth aged 15 to 19 and 33% of those aged 20-25 used cannabis, compared to only 13% of adults [59]. Although the average age of initiation in Canada is 18 years, many children's first exposure to cannabis is as young as elementary school [59,60]. According to recent literature, Canadian youth perceive recreational cannabis use to be widespread and relatively harmless [54,60]. In a qualitative study of 20 focus groups conducted across 6 cities in Canada, (n=77) youth indicated that cannabis was less harmful, and impairment due to cannabis was less concerning than alcohol and other substances [56]. Many reasons for cannabis use were cited including fitting in with peers or family, the availability and acceptability of the drug, and the drug's positive effects such as coping with stress. The reasons for not using cannabis included the fear of getting caught by parents or police and the stigma of being perceived as a 'drug user' [56]. Youth believed that cannabis would affect the brain in some capacity but had limited understanding of why or how [56]. Even though the risk for cannabis dependence among those who start using it in adolescence is approximately 16% [61,62], most youth were unaware that cannabis could be addictive [56]. Youth in this study used the internet to learn about cannabis and were overwhelmed with the quantity of information. They wanted unbiased information and suggested future prevention efforts should be interactive [56].

1.3 Cannabis, Cannabinoid Mechanism of Action, and Pharmacokinetics

Cannabis is traditionally derived from the plant *Cannabis sativa*. In Canada it is not classified as drug or a Natural Health Product (NPH) and therefore has no Drug Identification Number (DIN) or Natural Product Number (NPN) [63]. At least 489 distinct compounds are found in the leaves and flowering tops of cannabis plants, which harbour more than 120 different phytocannbinoids [63,64]. The most well recognized cannabinoids are delta-9-tetrahydrocannabinol (i.e., Δ^9-THC, THC), cannabinol (CBN), and cannabidiol (CBD). Other known cannabinoids include cannabigerol (CBG), cannabichromene (CBC), tetrahydrocannabivarin (THCV). Several other compounds such as flavonoids and terpenes are also found within the plant [65]. Each cannabis cultivar contains differing amounts of these compounds, and a variety of other factors such as soil and climate conditions, and various cultivation techniques can affect the pharmacologic constituents. Therefore, one of the major challenges with using cannabis as a therapeutic agent, is the fact that the exact chemical make-up varies considerably between strains and products.

Cannabis is available in many different formulations and there are four main methods of consumption: inhalation, oral, sublingual, or topical. Since inhalation is the fastest method of delivery this is the most common way to use it recreationally, although some people prefer this method for medical use as well. Inhalation generally refers to either smoking or vaping. Smoking involves burning the dried flower, leaf or bud and then using a joint, blunt (cigar), bong or pipe to inhale the constituents. Vaporization is similar to smoking, but the plant is not burned; instead, a vaporizer or vape pen or e-cigarette is used to heat the cannabis to a temperature to turn the active ingredients into a gas. Cannabis oil, flower, and leaf as well as solid cannabis extracts can be vaporized and sometimes carrier solvents and additives are used in the process, resulting in differing exposures and toxicities [66]. Smoking cannabis has been associated with multiple respiratory issues, including chronic bronchitis, airflow obstruction, asthma, secondary spontaneous pneumothorax, and lung cancer [67]. In general, vaping is thought to be a less harmful alternative to smoking. However, several cases of lung injury have been reported and termed EVALI (e-cigarette or vaping use-associated lung injury), which has been linked to adulterants, in particular vitamin E acetate [68].

Cannabis can also be consumed orally in the form of edibles, tinctures, capsules, or oils, or absorbed sublingually through dissolvable strips, sublingual sprays, or medicated lozenges or tinctures. In its raw state, the cannabinoids in cannabis are in their carboxylic acid forms and decarboxylation is required to convert tetrahydrocannabinolic acid (THCA) to THC and cannabidiolic acid (CBDA) to CBD, accomplished through light or heat via smoking, baking, or refluxing [69]. Therefore, eating raw plant material will not equate to the same therapeutic or psychoactive effect. Cannabis can be ingested orally or sublingually for both medical and recreational purposes. Cannabis used topically does not produce intoxication and therefore is only used for medical purposes.

In the 2021 Canadian Cannabis Survey, the most common types of cannabis acquired by medical cannabis users (n=844) were dried flower/leaf (50%), cannabis oil for oral use (49%) and edibles (31%) [70]. These products are available in different ratios of CBD and THC and the breakdown of product preferences for these individuals is as follows: 25% higher CBD and lower THC; 19% higher THC and lower CBD; 16% equal levels of THC and CBD; 17% CBD only products; 11% used a mix of different products [70]. In addition to cannabis plant derivatives, there are also some cannabinoids that are available with a prescription in Canada. Nabilone (Cesamet® and generics) is a THC analogue capsule that is indicated in the treatment of severe nausea and vomiting from cancer chemotherapy [71]. Nabiximols (Sativex®) is an oral/sublingual spray consisting of extracted THC and CBD in approximately a 1:1 ratio. It is used as an adjunctive treatment for advanced cancer pain, or spasticity or pain associated with multiple sclerosis [72]. A synthetic THC product dronabinol (Marinol®), and a purified plant derived CBD-only product cannabidiol (Epidiolex®), are available in the USA [73,74].

Cannabinoids act on the endocannabinoid system (ECS), which is a lipid signalling system that has a role in many physiological processes, including pain, inflammation, neurodevelopment, appetite, stress, metabolism, and reproduction [75]. This system, which is found in all vertebrates, is made up of cannabinoid ligands (i.e., endocannabinoids), cannabinoid receptors (CB1 and CB2), membrane transporters and the metabolic enzymes that modulate endocannabinoid synthesis and breakdown, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [75,76]. The naturally occurring cannabinoid ligands 'endocannabinoids' are derivatives of arachidonic acid. The two most prominent examples are arachidonoylethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), which act as the primary mediators of ECS signalling [77]. Other endogenous molecules may potentiate the effect of anandamide for example, through inhibiting FAAH-mediated degradation or allosteric effects on other receptors such as the transient receptor potential vanilloid (TRPV1) channel [78].

Anandamide and 2-AG as well as the phytocannabinoids (cannabinoids that are found in cannabis) bind to cannabinoid receptors with various affinities. The most prominent cannabinoid receptors, CB1 and CB2, are G-protein coupled receptors that act on presynaptic cells to reduce the release of a variety of excitatory and inhibitory neurotransmitters. The expression of anandamide and 2-AG seem to be exclusive to each other and are produced on demand by receptor-stimulated cleavage of their precursors [79]. Both anandamide and 2-AG show higher affinity for the CB1 receptor compared to CB2. Anandamide is a partial agonist with moderate affinity for endocannbinoid receptors, while 2-AG exhibits full agonistic properties with comparatively lower affinity [80]. CB1 receptors are primarily found in the brain, but are also present on immune cells, adrenal and pituitary glands, as well as in the bladder, GI, lung, and reproductive tissues. CB2 receptors, in contrast, are found within immune cells (spleen, leukocytes), as well as other locations such as the liver and nerve cells [80]. Given their ubiquitous nature, endocannabinoids are thought to help regulate a plethora of biologic processes. They play a role in anti-proliferative, anti-inflammatory, and anti-metastatic effects, as well as neurotransmitter, immune system, and mitochondrial function [81]. The ECS also plays a fundamental role in neurologic growth and development. During fetal life, endocannabinoids and the CB1 receptor regulate neural progenitor differentiation and guiding axonal migration and synaptogenesis. Neurotransmitter and behavioural functions are altered, similar to the effects of prenatal stress by perinatal manipulation of the ECS with cannabinoids or maternal cannabis consumption [82]. During adolescence, changes in endocannabinoid signaling contribute to the maturation of local and corticolimbic circuit populations of neurons, such as mediating the balance between excitatory and inhibitory neurotransmission within the prefrontal cortex, serving a critical function in establishing complex and adaptive cognitive and behavioral processing [83]. Changes in endocannabinoid signalling during this period of brain development and plasticity create a particularly sensitive environment. Manipulations and/or disruptions in endocannabinoid signalling during adolescence can lead to altered developmental trajectories of neural circuits governing emotional behaviors [83]. Regulation of synaptic communication occurs primarily through a retrograde signalling mechanism, whereby the endocannabinoids move retrogradely across the synapse and bind to presynaptic CB receptors, suppressing the release of neurotransmitters from the presynaptic terminal [80]. In addition to the CB1 and CB2 receptors, the cannabinoids may exert biologic activity through other targets, adding further complexity and contributing a myriad of effects. Anandamide, for instance, is an agonist at TRPV1, a receptor which is also activated by vanilloid ligands like capsaicin and noxious stimuli like heat and acids [80]. Cannabinoids may also bind to certain orphan receptors such as G protein-coupled receptor 55 (GPR55) [80].

Like the endogenous ligands anandamide and 2-AG, phytocannabinoids found within the cannabis plant bind to cannabinoid receptors and modulate the ECS. THC is a partial agonist at both CB1 and CB2 receptors and appears to exert its psychoactivity by stimulating CB1. Physiologic effects include anxiolysis, euphoria, heightened perception, increased sociability, sensation of time slowing, increased appetite, and decreased pain [80]. CBD, in contrast, is not intoxicating and it appears to oppose the effects of THC. CBD may impart other medical benefits such as reducing pain, inflammation, nausea, anxiety, and seizures [84]. It is a pleiotropic molecule which targets many receptors and pathways, and its mechanism remains to be fully elucidated. It does not appear to have agonistic properties at either CB receptor, and there is evidence that it is a negative allosteric modulator of CB1 receptors [85]. It likely contributes to indirect cannabinomimetic actions, however, through various other mechanisms. These may include increasing anandamide and 2-AG by decreasing the breakdown of intracellular endocannabinoid uptake through blocking the activity of FAAH; acting as an agonist of the TRPV1 channel; a partial agonist at serotonin 5-HT1A and 5-HT2A receptors; acting as a positive allosteric modulator of glycine receptors; as well as indirectly increasing the concentration of other biologically active compounds (e.g., inhibiting the uptake of adenosine, thymidine, glutamate, serotonin, γ-aminobutyric acid, dopamine and noradrenaline) [85]. The actions of other phytocannabinoids are even less well characterized. For example, CBG is a non-intoxicating partial agonist of CB1 and CB2 found in high concentrations in cannabis, which is a precursor of other important phytocannabinoids and may have analgesic and immunosuppressive effects [63,86]. CBN is a weak psychoactive compound that has higher affinity towards CB2 that may have immunosuppressive properties [63,86]. CBC does not have significant affinity for CB1 and CB2 receptors but influences the ECS by inhibiting anandamide uptake [63]. THCV is a CB1 receptor antagonist and CB2 receptor partial agonist that may have anticonvulsant, anti-nociceptive and potential anti-psychotic effects [63,87].

Most of the pharmacodynamic information on cannabis to date refers to the effects of THC and the pharmacokinetic profile of cannabis depends on the route of administration. Inhalation is the fastest route of absorption, with THC detectable in the plasma within seconds after smoking cannabis, which is likely why it is the preferred route of ingestion among non-medical users. Inhalent bioavailability ranges between 10 and 35% depending on the depth of inhalation, puff duration and breathhold [63]. Less data is available on the absorption of smoked CBD, but is thought to be similar to THC (~30%) [87]. The absorption of oral cannabis is slow and erratic, resulting in maximal plasma concentrations of THC usually after 60-120 minutes, but as late as 4-6 hours [63]. The oral bioavailability is estimated to be around 6% and is decreased by extensive first-pass metabolism. Active metabolites with potent psychoactive effects are also produced from this first-pass metabolism (e.g., 11-hydroxy-THC, 7-hydroxy-CBD) and contribute to the pharmacology of the cannabinoid [63,16]. A recent study in healthy adult subjects (n=12) indicated that CBD appeared rapidly in the plasma and the time to maximum concentration (t_{max}) was 4-5 hours after ingestion of a single dose of Epidiolex® 1500 mg

[88]. When administered sublingually (e.g., nabiximols), cannabinoid plasma concentrations peak in approximately 2-4 hours and blood levels are comparable to those seen with oral administration, although there is wide inter-individual variation [72].

Cannabinoids are highly lipophilic. They are taken up rapidly by highly perfused tissues and organs such as liver, heart, fat, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid, and pituitary gland, resulting in a rapid decrease in plasma concentration [84]. Accumulation then occurs in less vascularized tissues and finally body fat. They readily cross the blood-brain barrier and the placenta and pass into breast milk. The apparent (initial) volume of distribution for THC is equivalent to the plasma volume of about 2.5–3L, due to the high plasma protein binding that is estimated at 95-97%, but the steady state volume of distribution is about 10L/kg [84]. THC and its hydroxy metabolites are stored in fatty tissue and the slow redistribution of cannabinoids as well as enterohepatic recirculation lead to long elimination half-lives, ranging from 1.5 to 5 days for THC and even longer for metabolites [16,84]. The elimination half-life of CBD ranges between 2 to 5 days for chronic oral administration [89].

Cannabinoids are metabolized primarily by the liver and fall within the class of intermediate to high extraction ratio compounds (systemic clearance ranging from 600 to 1190 mL/min for THC and 960 to 1560 mL/min for CBD) [16,87,90]. Both THC and CBD are metabolized by the cytochrome P450 pathway (primarily CYP 2C19, 2C9 and 3A4) and are inhibitors of both CYP 3A4, 2C19 and 2C9 [91-95]. CBD may also be a substrate for CYP 1A1, 1A2, 2D6, 2E1, and 3A5 [92]. CBD, THC, and their respective metabolites may undergo subsequent glucuronidation by several UDP-glucuronosyltransferase (UGT) isoforms, which is controlled through specific cytochrome P450 oxidations as well as specific enzyme-substrate mechanisms [16,97]. Over 100 metabolites have been identified for both THC and CBD [63,98].

The decline of THC and CBD from the plasma is multi-phasic. After a pseudoequilibrium is reached between plasma and tissues, cannabinoids slowly rediffuse from body fat and other tissues. During this phase, plasma levels are very low making the true elimination from the plasma difficult to calculate [63]. THC is excreted primarily as acid metabolites within days and weeks. Approximately 20-35% of metabolites are eliminated by the kidney, 65-80% by biliary excretion and less than 5% of an oral dose is eliminated unchanged in the feces [63]. Renal elimination is achieved through glomerular filtration and tubular secretion; the lipophilicity of cannabinoids results in high tubular secretion but low renal excretion of the unchanged drug [63]. The elimination half-life for some cannabinoid metabolites also persists beyond the half-life of the parent molecule (e.g., THC-COOH, 11-OH-THC) and metabolites may be detectable for up to 12 days after a single dose of THC [63]. Urine screenings may fluctuate between positive and negative for several days since these metabolites do not decrease monotonously [63]. Less is known about the elimination of other bioactive cannabinoids.

1.4 Medical Cannabis and ADHD

As previously discussed in section 1.2, medical cannabis is increasingly being used to treat drug-resistant epilepsy, chemotherapy-induced nausea and vomiting, and other medical conditions such as autism spectrum disorder and spasticity in children, youth, and young adults. Another neurological condition that cannabis has been touted as a potential beneficial treatment is ADHD. ADHD is a highly prevalent mental health condition in children, youth and young adults and can persist into adulthood [99]. It is characterized by inattention and hyperactivity-impulsivity, and first line treatment typically involves pharmacotherapy with a stimulant medication and nonpharmacologic strategies, such as healthy diet, education, and cognitive and behavioral interventions [100]. First line treatments are effective in treating the core symptoms of ADHD (e.g., inattention and hyperactivity-impulsivity) in the majority of cases. However, many of these individuals experience additional comorbid disruptive behaviours and symptoms which are less likely to respond [101-103]. Effective treatments are urgently needed, as these symptoms can negatively impact an individual in all facets of life. For example, impulse aggression as a comorbidity of ADHD in children and adolescents can contribute to behavioral and disciplinary problems, decreased academic achievement, substance use challenges, and encounters with the justice system [104]. As such, caregivers are seeking out alternative solutions and turning to the social web for support. Some parents of children with ADHD have admitted to administering cannabis to their children for symptom management [105,106].

Despite the interest in medical cannabis as a treatment for ADHD the literature is sparse on this topic. Preclinical literature in animal models suggests of potential mechanistic possibilities. Brain imaging in patients with ADHD have indicated abnormalities in the neural networks linking the frontal cortex to the basal ganglia, and research suggests involvement of the dopaminergic system and abnormalities in the dopaminergic transporter (DAT) [107]. Castelli at al. discovered that endocannabinoid signalling in DAT mutant mice (which were hyperactive and paradoxically responded to both cocaine and methylphenidate, as with ADHD) was dramatically impaired, raising the possibility that cannabinoids may play a role in restoring this process [107,108]. Pre-treatment with cannabidiol (3 mg/kg) also increased social investigative behaviour in a Sprague-Dawley rat model of social withdrawal and hyperactivity due to treatment with MK-801 [109].

Clinical investigations regarding cannabis as a treatment option for ADHD are even more limited. Cooper and colleagues performed a (pilot) randomized controlled trial using Sativex Oromucosal Spray (1:1 Δ9-THC:CBD) or placebo in 30 adults with ADHD [110]. Doses during this 6-week trial were titrated to 4–8 sprays, and the mean number of active sprays used was 4.7± 3.3. In the Intent to Treat (ITT) analysis, cognitive performance measured by the QbTest indicated a pattern of improvement in the Sativex group, although this did not reach statistical significance (Est= 0.17, 95% CI-0.40 to 0.07, p=0.16, n=15/11 active/placebo). Nominally significant improvements were noted in the symptoms of hyperactivity / impulsivity (p=0.03), and trends towards improvement were found for inattention and emotional lability. All trends were strengthened when the per-protocol analysis was performed [110]. Notably, this study was conducted in adults. Presently, there are no trials on the efficacy or safety of medical cannabis in children, youth, or young adults with ADHD. Given the high prevalence and impact of this condition, and the widespread public interest in using medical cannabis, it's potential role in the treatment of ADHD requires further study.

1.5 Cannabis in Schools

Medical and recreational cannabis in children and youth and young adults bring about considerable challenges within the school environment. While recreational cannabis is no longer an illegal substance for adults in Canada, its use in the developing child is associated with significant risks, and harm reduction strategies are an important cornerstone of education within the school environment. Medical cannabis, in contrast, requires the need for addressing stigma and policies that support the medical use of cannabis for the health of the child.

The intersections of health, academic success, and education, along with the potential to reach most children and youth have made schools the ideal place for health education and promotion [111]. Recent changes to cannabis legislation in Canada and the increased public accessibility of recreational cannabis have created an urgent need to provide credible education about cannabis. From September to October 2017 the Government of Saskatchewan conducted a Cannabis Survey with the public to determine perceptions. [112]. Respondents indicated that they prioritized public education and awareness to address a variety of topics, including impaired driving laws and prevention, and health risks for children, youth, and young adults. Respondents also supported the use of campaigns and public education in schools and universities, among others [112].

The traditional approach to providing education about cannabis and other illegal substances has been to promote abstinence. In the context of legalized cannabis, however, messaging that focuses only on avoidance has little relevance and does not resonate with the experiences of youth [113-115]. Education is a clear determinant of health and information to reduce harms and provide tools and capacity for decision making is a more realistic approach to drug information [116]. Children, youth, and young adults require evidence-based information to make informed choices about cannabis consumption [116].

A variety of instructional approaches and learning theories can be applied in the classroom. In the traditional approach, the instructor aims to transfer knowledge passively through unilateral instruction [117]. Group activities may be performed, but discussion and exploration of the concepts are not encouraged. The learners are assumed to have the same baseline knowledge of the subject and are expected to learn the concepts at the same pace [117,118]. Behaviourism is based on the notion that learning occurs naturally through a series of positive and negative reinforcements which shape the process. This theory assumes that learning is passive, occurring through environmental responses of the learner which involve practice and repetition. Positive rewards are used to strengthen the behaviour, while negative reinforcements (i.e., removing something from the environment) decreased the likelihood that a behaviour will be repeated [119, 120]. The cognitive theory, in contrast, focuses on perception and the processing of information. This theory rejects the idea that learning is a passive process. It posits that the learner absorbs information, processes it, and then uses it to produce learning outcomes and fundamentally children learn by watching others [120, 121]. Constructivism is a learning theory that emphasizes the role of the learner and is based on the idea that learning is more effective when the knowledge is co-created [122]. This contrasts with passive learning as the learner is actively involved in the process. Since students require knowledge and skills to avoid harm when faced with influences to use drugs, the constructivist method is ideal for drug education [123]. This approach avoids setting the teacher up as the 'drug expert' and encourages learners to examine, elaborate on and question their own ideas and experiences, guided by available evidence and classroom discourse [123].

The role of cannabis as a medicine has evolved significantly rendering abstinence-based educational strategies even more irrelevant. Many children, youth and young adults will likely be acquainted with individuals or have family members who take cannabis for therapeutic purposes, and some youth may even be taking medical cannabis. Some individuals who take medical cannabis have reported a lack of support and stigmatization [124-126]. Cannabis education for young people should involve both harm reduction strategies for recreational use, as well as compassion and awareness of individuals taking cannabis for a medical purpose.

The evolving context of medical cannabis has added complexity to existing school regulations. Previously an illicit substance, cannabis has been unequivocally prohibited on school property. Anecdotal reports suggest that outdated school policies have added increased burden and barriers for children who require medical cannabis. The extent to which school policies are impacting medical care, however, are currently unknown.

1.6 Research Objectives

The objectives of this program of research were to: 1) Explore the treatment efficacy and pharmacokinetics of medical cannabis taken for a pediatric condition with perceived public benefit, but lack of evidence; 2) Undertake a scoping review on existing legislation, policy and protocols on medical cannabis in schools; 3) Describe the experiences of clinicians authorizing medical cannabis use for school-aged children and their caregivers; and 4) To create a cannabis risk reduction program that could be widely used in schools to promote meaningful engagement with youth.

1.7 Program of Research

This thesis is comprised of six separate publications, each addressing one of the research objectives. The first four publications are within the context of medical cannabis in children, youth, and young adults. Chapter 2 is mixed-methods proof-of-concept study protocol exploring the treatment efficacy, pharmacokinetics, and perceptions on ADHD and ODD. In Chapter 3, a case study describes the experiences and pharmacokinetics in three young adults taking medical cannabis for the treatment of their ADHD. Chapter 4 is a scoping review on policies about medical cannabis schools, while Chapter 5 and Chapter 6 detail the experiences of clinicians and caregivers regarding medical cannabis in schools, respectively. Finally in Chapter 7, the Real Education About Cannabis Health program development is described, which is within the context of recreational risk reduction.

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CHAPTER 2. PHARMACOKINETICS AND PERCEPTIONS OF CHILDREN AND YOUNG ADULTS USING CANNABIS FOR ADHD AND ODD: A MIXED-METHODS PROOF-OF-CONCEPT STUDY PROTOCOL

Mansell H, Quinn D, Kelly LE, Szafron M, Alcorn J. Pharmacokinetics and Perceptions of Children and Young Adults Using Cannabis for Attention-Deficit/Hyperactivity Disorder and Oppositional Defiant Disorder: Protocol for a Mixed Methods Proof-of-Concept Study. JMIR Res Protoc. 2021;10:e31281. doi: 10.2196/31281.

HM, DQ, LK, MZ, and JA designed the protocol. HM and JA drafted the manuscript. DQ, LK and MZ critically revised the manuscript, and have approved the final version to be published.

2.1 Abstract

Background: Despite the lack of evidence on the use of cannabis for the treatment of attention-deficit/hyperactivity disorder (ADHD), the growing perception that cannabis is safe has led more patients and caregivers to self-medicate. Some psychiatrists now authorize medicinal cannabis for patients with ADHD with features of oppositional defiant disorder (ODD) to curtail the unregulated (i.e., self-medicated) use of recreational cannabis or to offer a therapeutic option to those who continue to experience symptoms after exhausting all other treatment options.

Objective: This protocol aims to explore the perceived effectiveness and pharmacokinetics of cannabis in youth and young adults, who are currently taking it as part of their treatment plan for ADHD with features of ODD, under the supervision of a psychiatrist.

Methods: Patients between the ages of 12 and 25 years with a diagnosis of ADHD and features of ODD, who are currently taking cannabis herbal extract (at a Δ^9-tetrahydrocannabinol [THC]: cannabidiol [CBD] ratio of 1:20) as a treatment adjunct to stimulant pharmacotherapy will be recruited. A sample size of 10-20 individuals is estimated. The study interview will consist of (1) validated symptom rating scales (Swanson, Nolan, and Pelham-IV Questionnaire [SNAP-IV], 90-item; Patient Health Questionnaire, 9-item [PHQ-9]; and Screen for Child Anxiety Related Emotional

Disorders [SCARED] tool to measure symptoms of ADHD and ODD, depression, and anxiety, respectively); (2) a semistructured interview to probe the experiences of using cannabis; and (3) a cannabis side effects survey. A cannabis product sample as well as 2 blood samples (a trough level and 2-hour postdose level) will be collected to measure plasma concentrations of cannabinoids and relevant metabolites (THC, CBD, 11-hydroxy-THC, 7-hydroxy-CBD, cannabichromene, and 11-nor-9-carboxy-THB) using liquid chromatography–tandem mass spectrometry (LC–MS/MS). Self-report rating scales (SNAP-IV, SCARED, and PHQ-9) will be scored in accordance with standard protocols and compared to retrospective scores obtained from the participant's chart. Demographic variables (age, weight, and race), symptom scores, and blood levels (peaks and troughs) of THC, CBD, CBC, and metabolites will be summarized using descriptive statistics. Relationships between plasma concentrations and symptom scores will be determined using analysis of variance, and multiple regression analysis will be performed to determine associations between plasma concentrations and demographic variables (age, weight, and ethnicity). The qualitative data will be audio-recorded and transcribed and organized into themes.

Results: The protocol was approved by the Biomedical Research Ethics Board at the University of Saskatchewan (protocol #1726) and recruitment began in May of 2021.

Discussion: This proof-of-concept study will explore the potential treatment effectiveness of medical cannabis in participants with ADHD and ODD using a mixed methods approach to inform future research in this area.

2.2 Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental health conditions in children, with an estimated worldwide prevalence of 7.2% [1]. This chronic neurobehavioral disorder is characterized by inattention and hyperactivity-impulsivity and affects both children and teens, with up to 60% of those affected exhibiting symptoms into adulthood [2]. Treatment of ADHD typically involves nonpharmacologic strategies (e.g., healthy diet, education, and cognitive and behavioral interventions), and pharmacologic therapy with a psychostimulant (e.g., methylphenidate) [3]. While stimulant pharmacotherapy is effective for treating the core symptoms of ADHD, in approximately 70%-90% of cases, symptoms of aggression are less likely to respond. Approximately 35%-65% of children with ADHD exhibit comorbid disruptive behavior disorders (DBDs; oppositional defiant disorder [ODD], or conduct disorder) [4,5], and a substantial number continue to exhibit aggressive and disruptive behaviors even after stimulant treatment [4-6]. The consequences of inadequately treated aggressive and disruptive behaviors are significant; these children are more likely to have encounters with the justice system, deficits in academic achievement, behavioral and disciplinary problems, and substance use challenges [7].

Cannabis use and ADHD

The growing perception that cannabis may be useful for alleviating ADHD symptoms has motivated individuals to use cannabis without the necessary evidence to support its use and without clear guidance on appropriate dosing [8,9]. A recent study of internet-based discussions about the effects of cannabis on ADHD found at least 3 times as many comments advocating for cannabis' therapeutic benefits, compared to comments regarding harm or lack of efficacy [10]. Moreover, several parents of children with ADHD have admitted to administering cannabis to their children for symptom management [8,11].

Some adults with ADHD have reported benefits from using cannabis. These benefits include feeling calmer, improved sleep, and the ability to sustain focus [12]. Patients with ADHD typically use cannabis "to improve their mood and sleep" rather than "to get high" [13]. Cannabinoids act on the endocannabinoid system, which is a signaling system consisting of 2 receptor subtypes (CB1 and CB2). ADHD involves a dysregulation of dopamine, and stimulant pharmacotherapy works by blocking the reuptake of dopamine as a result of the inhibition of noradrenergic areas in the prefrontal cortex [14]. CB1 receptors also interact with the dopaminergic system, and it is hypothesized that the modulation of endocannabinoids in the medial prefrontal cortex and the ventral tegmental area may lead to regulation of the impulsive action and restraint [15,16]. Several other neurotransmitters, such as glutamate, γ-aminobutyric acid, and *N*-methyl-D-aspartate, as well as CB2 receptors can interact with endocannabinoids and may contribute to the modulation of impulsivity [15-17].

Co-occurring substance use is one of the most common problems associated with ADHD. Children with ADHD are at an increased risk for both using cannabis and having a cannabis use disorder, and these youth are nearly 3 times more likely to report cannabis later in life compared to the general population [10,18]. Whether or not potential harms associated with substance use are worse for youth with ADHD is currently unknown.

The self-medication theory is one possible theory to explain the increased risk of substance misuse in some patients [19,20]. This hypothesis, which is a theory about addiction, originally focused on why and how individuals were drawn to heroin and cocaine [19]. In 1997, it was updated to consider a variety of other applications [20]. Based on decades of clinical observation, it proposes that patients consume drugs in an effort to cope with the illness or treatment side effects [19,20]. In the case of ADHD, individuals may self-medicate to alleviate negative emotionality, such as anger, sadness, anxiety, and inadequate emotional regulation [21]. In medicine, the decision to initiate a medication or other treatment is based on the theoretical gains in therapeutic benefits weighed against the potential harms [22]. Observational studies indicate that cannabis may improve symptom management and decrease side effects associated with prescription medication, or as a substitute for alcohol and illicit drugs [16,23,24]. Nonmedical cannabis use has also helped to decrease cocaine dependence in a study of patients with ADHD [25]. In this capacity, cannabis substitution could be considered a harm reduction strategy [22]. Some psychiatrists within our institution have now resorted to prescribing medicinal cannabis for patients with ADHD and ODD who were using unregulated cannabis recreationally, or “self-medicating,” or among those who continue to experience symptoms after exhausting all other treatment options. The dearth of evidence regarding cannabis use for ADHD bespeaks an urgent need to determine whether cannabis use is safe and effective in these individuals

Goal of the study

The goal of this pilot study is to examine the real-world effectiveness by comparing changes in their disease-related symptoms before and after beginning treatment with medical cannabis, using validated assessment scales for ADHD, ODD, depression, and anxiety. We will characterize their experiences with using medical cannabis by way of a semi structured interview and cannabis side effects survey. Furthermore, blood levels of commonly found cannabinoids in cannabis in children and young adults who are currently taking medical cannabis for the treatment of their ADHD and ODD under the care of a pediatric psychiatrist will be correlated with symptom scores and demographic variables (age, weight, and ethnicity). Finally, a sample of the participant’s cannabis will be analyzed through liquid chromatography–tandem mass spectrometry (LC–MS/MS) to confirm its chemical composition.

2.3 Specific Objectives and Hypotheses

Hypothesis 1: Patients who use medicinal cannabis perceive improvements in ADHD and ODD symptoms.

Hypothesis 2: Improvements in self-reported symptom scores associate with higher plasma levels of cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) and their bioactive metabolites.

Primary Objectives:

1. Examine the changes between self-report ADHD scores (as measured by the symptom scores of the Swanson, Nolan, and Pelham-IV Questionnaire [SNAP-IV, 90-item]) before (retrospectively) and after the initiation of medical cannabis.

2. Examine potential associations between steady-state plasma concentrations of CBD, THC, cannabichromene (CBC), and well-known metabolites in children with symptom scores of the SNAP-IV (90-item).
3. Characterize the experiences of participants using medical cannabis.

Secondary Objective:

1. Examine potential associations between self-reported symptom scores from other validated ADHD assessment tools (Screen for Child Anxiety Related Emotional Disorders [SCARED] rating scale, and Patient Health Questionnaire, 9-item [PHQ-9]), and steady-state plasma concentrations of CBD, THC, CBC, and well-known metabolites in children using cannabis for ADHD with ODD.

2.4 Methods

Study Design and Inclusion Criteria

An observational, mixed methods, proof-of-concept study will be undertaken at 1 center in Saskatchewan. The protocol was designed to minimize face-to-face contact, so the study can be performed during the COVID-19 pandemic. Patients with ADHD and ODD who are currently taking cannabis herbal extract (at a THC:CBD ratio of 1:20) as a treatment adjunct to stimulant pharmacotherapy are eligible to participate. Participants are between the ages of 12 and 25 years; have a diagnosis of ADHD in accordance with Diagnostic and Statistical Manual of Mental Disorders (5th edition) with features of ODD; are stabilized on medical cannabis herbal extract (at a THC:CBD ratio of 1:20); and have been deemed safe to participate by the study physician. Participants under the age of 18 years must also have the permission of a guardian to participate. We acknowledge that some patients with ADHD may have comorbid mental health disorders, such as autism spectrum disorder. For the purpose of this study, though, we will only enroll participants who are functionally able and willing to provide assent. We will aim to enroll at between 10 and 20 participants in this pilot study.

Enrolment and Consent

Potential participants and their caregivers will be identified and initially contacted by the study physician (DQ) through his childhood and adolescent psychiatry practice at the Saskatchewan Health Authority (SHA) in Saskatoon (Saskatchewan, Canada). If the family is interested in learning more, their contact information will be forwarded to a research team member who will follow up with the family. Potential participants (and guardians, if applicable) who express interest will be provided with a copy of the consent form and the study information reviewed. If the participant (and caregiver, if applicable) opts to participate, logistics will be arranged and informed consent taken.

Study Interview

Overview

A study interview will be performed at a mutually convenient time for the participant (and caregiver, if applicable) and research team member. The interviews are expected to last approximately 40-60 minutes each and will be conducted via Cisco WebEx or phone, depending on the participant's preference. If the participant requires a break during the interview, we will accommodate this need. The interviews will be audio-taped, and notes recorded by the researcher, but all information gathered from the participant will be kept confidential. Demographic information is collected, including cannabis product and dosing regimen, age, sex, clinical diagnosis, ethnicity, other medications, and participants' self-reported height and weight. Self-reported rating scales are used to measure participants' current symptoms of ADHD and debility, and a semistructured interview will be used to explore their experiences of cannabis use.

Self-report symptom rating scales

The SNAP-IV (90-item) is a revision of the original SNAP questionnaire [26,27], which contains items from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria to assess inattention (items 1-9), hyperactivity/impulsivity (items 11-19), and ODD (items 21-28). Items have also been added to summarize the Inattention, Hyperactivity/Impulsivity, and ODD domains (items 10, 20, 29, and 30), as well as items representing a general index of childhood problems (items 31-90). Each item measures the frequency or severity of a symptom or behavior, on a Likert scale of 0-3 (0=not at all and 3=very much). This instrument has been shown to have good reliability and validity in different study samples [28].

The PHQ-9 is a 9-item tool used for screening, diagnosing, monitoring, and measuring the severity of depression [29]. Each item is scored on a Likert scale of 0-3 (0=not at all and 3=nearly every day). The items are summed to equal a total between 0 and 27, with higher scores equating to a higher level of debility [29].

The SCARED tool, which assesses anxiety symptoms, consists of 41 items and 5 factors that parallel the DSM-IV classification of anxiety disorders [30]. Each item is scored on a Likert scale of 0-2 (0=not true or hardly ever true and 2=very true or often true). A score of ≥25 may indicate the presence of an anxiety disorder and scores higher than 30 are increasingly specific [30].

Cannabis use questions
A semi-structured interview guide will be used to characterize the perceptions of participants (and guardians, if applicable) of cannabis treatment. The interview guide was drafted a priori by the research team and was piloted on 3 patients who use cannabis therapeutically. The interview consists of 6 open-ended questions, which explore participant's life circumstances before initiating medical cannabis, contributing factors for choosing this treatment*,* how (if at all) things have changed, what concerns (if any) might exist about treatment, and how the participant obtains the medical cannabis (Table 2.1). The interviews will be flexible, depending on the participant's responses and probes will be used to delve further into potential areas of interest. No time restrictions will be placed on the interview. Rather, the conversation continues until data saturation is reached, and no further information is offered from the participant. Field notes will be taken throughout the interview to capture nuances of the conversation. Finally, a cannabis side effect survey [31] will be administered, which capture potential side effects experienced from taking cannabis within the previous week. Potential side effects in this survey are categorized under the domains of cognitive, physiological, psychological, movement, and artistic/social, and response choices for each item include "yes," "no," or "uncertain."

Table 2.1 Semi-structured interview guide

	This set of questions will help us learn more about your experience with *Cannabis*. Please note, you do not have to answer any questions you do not feel comfortable with.
1	Tell me about your life growing up with ADHD prior to taking medical *Cannabis*?
2	What led you to choose medical *Cannabis/* what was the reason for starting medical *Cannabis*?
3	How have things changed for you (if at all) since beginning *Cannabis*?
4	What concerns (if any) might you have about taking medical *Cannabis*?
5	Tell me how you get the *Cannabis*?
6	What else do you want me to know about your experience with *Cannabis* or ADHD?

Blood Collection

Within 1 week of the interview, the mobile laboratory will visit the participant's residence to obtain 2 blood samples for evaluation of the plasma levels of CBD, THC, CBC, and active metabolites. Measured metabolites will include 11-hydroxy-Δ^9-THC (11-OH-THC) and 7-OH-cannabidiol. A trough level (immediately before the morning cannabis dose) will be collected to represent the minimum steady-state plasma drug concentration ($C_{SS,min}$), while a 2-hour postdose level is collected to represent the maximum steady-state plasma drug concentration ($C_{ss,max}$; where therapeutic effect should be the highest) [32,33]. Blood samples (1 mL each) will be collected into BD Vacutainer Barricor tubes [34] and centrifuged at 2000 × g for 5 minutes to separate plasma. Samples will be subsequently transferred to Eppendorf Protein LoBind microcentrifuge tubes and transported on ice, until they reach the laboratory for storage in a –80°C freezer.

Concurrent medications will be continued by the participant as per usual. No dietary restrictions are imposed on the day of the pharmacokinetic analysis, to capture the real-world situation of patients using cannabis herbal extract as an adjunct treatment to stimulant therapy.

Cannabis Sample Collection

Participants are provided with an option to have a small sample (<0.5 mL) of their cannabidiol oil collected on the day of the blood collection, to be analyzed in the laboratory. The purpose is to confirm the composition of the cannabis product. The results of this analysis will be communicated back to the participant.

Data Analysis

Sample Size Determination and Power Calculation

Since there is an absence of literature in this area, with this proof-of-concept study, we aim to recruit as many subjects as possible up to a maximum of 20 participants. The data obtained from this pilot analysis will be used to inform future clinical studies.

Cannabis Analysis

The medical cannabis product sample will be analyzed for the major cannabinoids in the product (eg, THC, CBD, and CBC). The plasma concentrations obtained from the participant will undergo analysis for the major cannabinoids and their relevant metabolites (THC, CBD, 11-OH-THC, 7-OH-CBD, CBC, and 11-nor-9-carboxy-THC (THC-COOH) using LC–MS/MS. This method has been previously developed and validated within our institution [35] in accordance with the guidelines of the Food and Drug Administration [36].

Quantitative Analysis

The self-reported rating scales (SNAP-IV, SCARED, and PHQ-9) will be scored in accordance with standard guidelines. Changes in rating scores will be determined by subtracting the baseline score (obtained prior to cannabis initiation) available in the participant’s medical chart, from the final score obtained during the interview. Demographic variables (age, weight, and racial background), symptoms scores, and blood levels (peaks and troughs) of THC, CBD, CBC, and metabolites will be summarized using descriptive statistics. Adverse effects will be summarized descriptively or listed. Differences between plasma concentrations and symptom scores will be determined using analysis of variance (ANOVA) and multiple regression analysis will be used to determine associations between plasma concentrations and demographic variables (age, weight, and racial background). Spearman ρ will be used to calculate correlation coefficients. To control for the increased type I error resulting from these multiple comparisons, the level of significance will be set to $P \leq .01$. Statistical analyses will be performed using SPSS (version 27, IBM Corp).

Qualitative Analysis

Audiotapes from the interviews will be transcribed verbatim and the data will be input into NVivo qualitative software. The data will be coded by one of the study investigators and will be reviewed by one of the primary investigators. Discrepancies between the investigators will be resolved through discussion and debate and the second primary investigator will weigh in if needed. The data will be organized into common themes and summarized.

2.5 Results

The protocol was approved by the Biomedical Research Ethics Boards at the University of Saskatchewan (protocol #1726). Recruitment began in May of 2021.

2.6 Discussion

Legalization of recreational cannabis occurred in Canada in October 2018. The increased public accessibility, coupled with perceptions that cannabis is "natural" and perhaps "safer" than some of the other available pharmacotherapeutic agents [8,9], has increased the probability of cannabis use in this population, despite an absence of evidence on efficacy or safety in youth or young adults.

At the time this study was designed, only 1 controlled clinical trial was published on the use of cannabis in ADHD. Cooper et al [37] performed a (pilot) randomized controlled trial using Sativex Oromucosal Spray (1:1 THC:CBD) or placebo, in 30 adults with ADHD. Participants in the Sativex group demonstrated a pattern of improved cognitive performance as measured by the QbTest, nominally significant improvements in symptoms of hyperactivity/impulsivity (P=.03), and trends toward improvement for inattention and emotional lability. All trends were strengthened when the per-protocol analysis was performed [37]. Case reports have also described the beneficial effects of cannabis on ADHD symptoms [16,38].

Controlled clinical trials are clearly needed to determine the impact of cannabis use on ADHD symptoms in youth and young adults. Understanding the impact of pharmacotherapy is of particular importance in the pediatric population, where development may be adversely and unpredictably impacted by drug therapy [39]. However, pilot studies need to precede interventional studies to understand feasibility and to glean important information about the pharmacokinetics of cannabis in the pediatric patient population to guide dosing strategies.

While the small sample size of this pilot study will preclude treatment recommendations, the importance of this study should not be understated. Exploring the real-world effectiveness and pharmacokinetics of cannabis in a cohort that is already taking cannabis is the most ethical way to gather the necessary information for initiating a research program in this area. If the results from this pilot study are positive, our future work will include a single dose pharmacokinetic study and eventually a randomized controlled trial.

2.7 Conclusions

Novel treatment strategies are needed for patients who experience symptoms of ADHD and ODD despite stimulant pharmacotherapy. Some desperate families have resorted to using cannabis, despite the lack of safety or efficacy data. This pilot study will be the first to explore the real-world effectiveness, perceptions, and pharmacokinetics of cannabis in children and young adults, and the results will guide future study in this area.

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CHAPTER 3. CANNABIS FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: A REPORT OF 3 CASES

Mansell H, Quinn D, Kelly LE, Alcorn J. Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder: A Report of 3 Cases. Med Cannabis Cannabinoids. 2022 Jan 13;5(1):1-6. doi: 10.1159/000521370.

HM contributed to the research design, data collection and manuscript writing. DQ, LEK, and JA contributed to the research design and reviewed and revised the manuscript.

3.1 Abstract

Attention deficit hyperactivity disorder (ADHD) is a chronic neurobehavioural disorder that is highly prevalent in children and adults. An increasing number of patients with ADHD are self-medicating with cannabis, despite a lack of evidence on efficacy and safety. This case report describes three males (ages 18, 22 and 23) who have integrated cannabis into their treatment regimen with positive results. Semi-structured interviews conducted with the patients describe subjective improvements in symptoms and on quality of life. Improvements on validated rating scales conducted post-cannabis initiation, compared to pre-cannabis initiation obtained from the medical chart, corroborated their personal accounts. Scores on the PHQ-9 (measuring depression) improved by 8 to 22 points (30-81%) and the SCARED (measuring anxiety) ranged from 0 to 27 points (up to 33%). Improvements on the CEER-9 scale (measuring regulation) ranged from 2 to 7 points (22-78%), and the 9-item SNAP scale (measuring inattention) showed improvements of 2 to 8 points (7-30%). Mild adverse events including short-term memory problems, reported dry mouth and sleepiness were reported. Blood samples were also collected from the patients to determine the plasma concentrations of the cannabinoids and relevant metabolites before and after a cannabis administration. After cannabis use, the plasma levels for CBD and THC ranged from 0 to 15.29 ng/ml and THC 1.32 to 13.76 ng/ml, respectively. Cannabinoids, however, were not detected prior to dosing, suggesting that cannabis played a complimentary role in the therapeutic regimen of these three patients. Clinical trials are recommended to confirm the efficacy of cannabis in the treatment of ADHD.

3.2 Introduction

Public acceptance of medical cannabis for the treatment of chronic conditions has increased despite a lack of scientific evidence for safety and efficacy [1,2]. In Canada, access to both medical and recreational cannabis is now legal, and self-medication with cannabis for a variety of symptoms has become more prevalent. Evidence-based information has not kept pace with the legislation and many clinicians remain reluctant to authorize cannabis until robust evidence is available to guide treatment [3]. Unfortunately, the limited evidence base may persist due to key challenges such as the difficulty in conducting randomized and placebo-controlled trials with cannabis [4] and the significant variability in cultivars. With more than 489 distinct compounds in the leaves and flowering tops of cannabis plants, which include at least 120 different phytocannbinoids and other entities such as flavonoids and terpenes [5,6], cultivars demonstrate important differences in therapeutic effect. Even within a given cultivar, soil and climate conditions and various cultivation techniques can influence its constituent bioactive components. The method of consumption or route of administration further impacts the pharmacokinetics and therapeutic effects of cannabis [7].

Attention deficit hyperactivity disorder (ADHD) is one such condition where few clinicians authorize cannabis but interest in self-medication is high. ADHD is a chronic neurobehavioural disorder characterized by inattention and/or hyperactivity-impulsivity with a prevalence of approximately 7% in children and 2.5% in adults [8,9]. Over half of children and adults with ADHD have comorbid psychiatric conditions, such as sleep disorders, mood and anxiety disorders, and oppositional defiant disorder (ODD) [10,11]. In addition to the first line pharmacotherapy with stimulants, internet discussions frequently indicate and advocate use of cannabis for relief of ADHD symptoms [12-14]. In one study, at least three times as many online comments attested for its therapeutic benefits in comparison to harm or lack of efficacy [14]. Despite the public interest and anecdotal reports, we only found one study on the use of cannabis in ADHD which compared Sativex Oromucosal Spray to placebo in a pilot study of 30 adults, where participants in the intervention group showed no difference in the primary outcome (cognitive performance as measured by the QbTest), but improved symptoms of hyperactivity/impulsivity (secondary outcome, $p = 0.03$) [15]. While this study investigated a commercially available product [containing 1:1 cannabidiol (CBD): Δ^9-tetrahydrocannabinol (THC)], a product available in some countries by prescription, many patients are self-medicating with unlicensed products in a variety of formulations [12-14].

In the absence of scientific data, case reports are valuable for presenting new observations, generating hypotheses, and providing in depth examinations of a subject of study as well as its related contextual conditions [16]. In this case report, we identified patients from a psychiatry practice who were prescribed ADHD medications but also self-medicated with cannabis. We explored treatment efficacy and patient perceptions of cannabis use. Since no literature exists to provide guidance for cannabis dosing in patients with ADHD, we also collected patient blood samples to determine plasma concentrations of the cannabinoids and relevant metabolites

3.3 Methods

Three patients who were taking cannabis for symptomatic relief of their ADHD participated in telephone interviews conducted by one of the authors (HM). The patients were previously diagnosed using the DSM-V criteria. The interviews lasted between 39 and 59 minutes. To characterize the patient's experiences of taking cannabis and its perceived efficacy, a semi-structured interview guide facilitated a discussion about the patient's life prior to initiating cannabis, the decision/reasons for starting it, how (if at all) things have changed since initiating cannabis, logistics on consumption and access, and what (if any) concerns they might have about cannabis. A cannabis side effect survey [17] inquired about potential cannabis side effects experienced by the patients, using the time frame of the previous week.

Self-report symptom rating scales, including the Swanson Nolan and Pelham (SNAP-IV) (90-item) [18], the Screen for Child Anxiety Related Emotional Disorders (SCARED) [19], and Patient Health Questionnaire (PHQ-9) [20], were performed during the interviews as a measure for treatment efficacy. The SNAP-IV rating scale contains 90 items from the DSM-IV criteria which assess inattention, hyperactivity/impulsivity, and oppositional defiant disorder, as well as items representing a general index of childhood problems. This tool, which is a modified version of the original SNAP questionnaire [18,21], consists of Likert scale questions that measure the frequency/severity of a symptom or behaviour. The items are scaled from 0-3 (0 = “not at all”, 3= “very much”), and the tool has had good reliability and validity in different study samples [22]. The SCARED rating scale and PHQ-9 assessed symptoms of anxiety and depression, respectively. The three rating scales were summed according to standardized methods [18-20] to achieve a composite score, with higher scores equating to higher levels of debility. Baseline symptom scores obtained before cannabis was initiated were collected from the patient’s medical chart and subtracted from the totals, producing an indicator of symptom change. ADHD inattentive symptoms were measured using items 1-9 of the SNAP-IV, while emotional regulation and irritability were measured using the Clinical Evaluation of Emotional Regulation-9 (CEER-9) method, whereby items 21, 23, 25, 26, 28, 34, 38, 39 and 54 from the SNAP-IV questionnaire were converted to a binary score, (0= not at all, 1=very much) [23].

Two blood samples were obtained from each patient by the mobile laboratory to allow quantification of plasma concentrations of cannabinoids and relevant metabolites (THC, CBD, 11-hydroxy-THC, 7-hydroxy-CBD, cannabichromene, 11-nor-9-carboxy-tertrahydrocannabinol). The samples were collected in BD Vacutainer® Barricor™ tubes [24], centrifuged to separate plasma, transferred to Eppendorf™ Protein LoBind microcentrifuge tubes and stored in a -80°C freezer until they were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The method was previously developed and validated within our institution [25] according to FDA guidelines [26].

Written informed consent was obtained from patients for publication of the details of their medical case and ethics approval for data collection was approved the by Biomedical Research Ethics Boards at the University of Saskatchewan (#1726).

3.4 Case Presentations and Patient Perceptions of Cannabis

The case presentations as described in this section represent an account of the patients' testimonials, with information verified from the medical charts. The patients had the opportunity to review these descriptions for accuracy prior to publication.

Patient 1: A 23-year-old white male with ADHD and generalized anxiety disorder decided to use cannabis after learning of its effectiveness for ADHD online. Medicated with methylphenidate, pregabalin, fluoxetine and clonidine, he first tried cannabis in his teens. He used it periodically as cannabis improved his focus. He eventually consulted his physician and received an authorization for medical cannabis in a CBD:THC 20:1 ratio, twice daily. He currently alternates between taking cannabidiol oil orally or smoking flower or bud. Although he realizes oil is less harmful for his lungs and more suitable in some situations, he feels smoking is more relaxing. He describes cannabis as a 'really good helping hand' to compliment his other medications and finds he is more open with others, less anxious, and his emotions are less exaggerated. Cannabis has improved his ability to maintain focus. Regarding his life before cannabis, he says "I was all over the place, bouncing off the walls kind of thing. Couldn't really stay on one task for long. I'd get halfway to three quarters done one task and then move on and do a completely different task." Cannabis, as he describes, "levels him out,"and he can complete tasks more efficiently. Although his family members' reaction to his cannabis have been mixed (with some individuals very supportive and others skeptical), he believes they have all noted a positive impact on his demeanor. Since taking cannabis regularly, he has found and maintained successful employment at a job away from home. The cost of medical cannabis is unaffordable, so he obtains recreational cannabis at half the cost.

Patient 2: A Caucasian male with ADHD has taken methylphenidate off and on since the third grade. He disliked being medicated with stimulants because he felt they changed his personality and he continued to struggle with emotional regulation. At age 17 he was prescribed lithium and he decided to start cannabidiol oil (CBD:THC in a 20:1 ratio) once daily (at bedtime) after a family member recommended it to him. Taking cannabis, he says, makes him feel more relaxed, helps him to focus and to feel more 'himself'. The combination of lithium (300 mg at bedtime), cannabis (l mL at bedtime) and a good support system he says, have completely changed his life. Previously he lacked motivation, did not do well in school, and was admitted for psychiatric care. Since starting cannabis, he was successfully weaned off his other medications for ADHD (takes only lithium for depression, and cannabis) and has completely turned his life around. Regarding his life before cannabis he says, "I was definitely a lot more jittery and stuff when I was in school…It [cannabis] helped me to focus a lot more and it helped me ease off my ADHD meds actually". He works full time and runs a business, sets long term goals for future, and has made many new friends, which has improved his social life.

Patient 3: A 22-year-old male diagnosed with ADHD when he was 20 and started self-medicating with cannabis. He had no prior history of cannabis use, but with dispensaries opening in Canada and a family member who was considering it for anxiety, he decided to try it as well. He feels that cannabis calms him, helps him to slow down and focus on one thing, and to sleep at night. He believes that cannabis works synergistically with his other medications (dextroamphetamine, amantadine, pregabalin) to improve his concentration, and control his racing thoughts and anxiety and emotions. Prior to treatment with this combination and as a child, he describes, "the lashing out was really bad, not listening to adult figures. And emotions…And forgetting where I placed stuff. I lost my wallet and keys *a lot* growing up." Having experimented with various strains, ratios, and methods of consumption, he prefers an Indica blend that is higher in THC and lower in CBD. Sativa caused him to be a bit more hyperactive and increased his anxiety, whereas an Indica dominant blend helps him to cool down. He is currently smoking a product that has a CBD:THC ratio of 0:18-19 at bedtime and says that this formulation does not make him feel intoxicated. Dabbing (which has a higher concentration of THC), however, has too much THC and puts him in an 'unmotivated funk'. He has tried edibles and oils, but they fail to improve his sleep. He avoids vaping because with his addictive personality and convenience of vaping he found that he vaped more than just at night. He obtains his supply from a recreational cannabis dispensary where it is most affordable.

3.5 Rating Scale Changes Pre- and Post-initiation of Cannabis

Table 3.1 presents the rating scales obtained from the patient's medical record and on the day of the interview. These scores were (respectively) obtained before and after the patients used cannabis regularly. Consistent with the testimonials, all three patients experienced positive improvements on the measures for depression, emotional regulation, and inattention. The scores from patients 1 and 2 also indicate an improvement in the SCARED, which measures symptoms of anxiety.

Table 3.1 Rating scale scores obtained from 3 ADHD patients' medical charts prior to and after initiation of cannabis

			PHQ-9	**SCARED**	**CEER-9**	**SNAP**	**SNAP-IV (90-item)**
	Construct measured		Depression	Anxiety	Emotional Regulation	Inattention	Multiple
	Scale range		[0-27]	[0-82]	[0-9]	[0-27]	[0-270]
Patient	**Timeframe**	**Date**					
1	**Pre-Cannabis**	March 2020	22	77	9	24	n/a
	Post Cannabis	July 2021	0	50	2	16	127
2	**Pre-cannabis**	Sept 2019	9	28	6	n/a	n/a
		Nov 2019	12	27	7	15	n/a
	Post-cannabis	May 2021	1	19	4	9	57
3	**Pre-cannabis**	March 2020	13	30	5	7	n/a
		June 2020	n/a	n/a	3	18	n/a
	Post-cannabis	July 2021	5	30	0	5	46

PHQ-9 - Patient Health Questionnaire-9; SCARED - Screen for Child Anxiety Related Emotional Disorders; CEER-9 – Clinical Evaluation of Emotional Regulation-9; SNAP-IV (90-item)- Swanson Nolan and Pelham rating scale; n/a - data not available in chart

3.6 Cannabis Side Effects

All patients reported mild side effects from cannabis use. Patient 2, who consistently takes oil orally, experienced short-term memory problems. Patients 1 and 3, who alternate between oral and inhalation routes, reported dry mouth and sleepiness. Patient 1 reported occasional experiences of constant desire to eat, more forgetfulness and apathy, and patient 3 reported an altered sense of time.

3.7 Blood Sample Analysis

Two blood samples were taken at home just prior to and 2 hours after cannabis administration were taken from each patient to quantify plasma concentrations of major cannabinoids and relevant metabolites (Table 2). Each patient self-reported their cannabis product and was not verified by chemical analysis. None of the patients had detectable plasma concentrations of any of the cannabinoids tested during the pre-dose level (trough), which represents the time when plasma levels are the lowest. The post-dose level, which is intended to represent the maximum plasma cannabinoid concentration should be collected at approximately 30 minutes after smoked cannabis and 2 hours for edible formulations [6]. Patient 1, who alternates between routes, ended up smoking cannabis on the day the mobile lab was scheduled to draw levels at 2 hours post. Therefore, patient 1's plasma concentrations are not representative of the true maximum.

Table 3.2. Plasma concentrations of cannabinoids and relevant metabolites obtained from blood samples of 3 ADHD patients self-medicating with cannabis.

Patient	Self-reported product and route	Patient Sample	CBD (ng/mL)	6-OH-CBD (ng/mL)	7-OH-CBD (ng/mL)	THC (ng/mL)	11-OH-THC (ng/mL)	THC-COOH (ng/mL)	CBC (ng/mL)
1	CBD:THC 20:1 flower smoked	Predose	ND	ND	ND	ND	ND	ND	ND
		Postdose (2 hr)	BLOQ	ND	ND	13.76	6.30	248.56	ND
2	CBD:THC 20:1 oil 1mL oral	Predose	ND	ND	ND	ND	ND	ND	ND
		Postdose (2 hr)	15.29	ND	ND	1.32	0.72	2.50	ND
3	CBD:THC 0:19 flower smoked	Predose	ND	ND	ND	ND	ND	ND	ND
		Postdose (30 min)	ND	ND	ND	7.65	0.60	14.51	ND

BLOQ – Below the limit of quantification; ND – Not detected

3.8 Discussion/Conclusion

We describe three patients with ADHD who added cannabis to their treatment regimen and experienced positive therapeutic effects. The improvements in their symptoms and quality of life were substantial, such as the ability to keep emotions in check (three patients) or to obtain and excel at a new job with more responsibility (two patients). Objective measures accompanied these narratives with all three patients experiencing improvements in validated rating scales for measures of mental health. Scores on the PHQ-9, which measure depression, improved by 8-22 points (30-81%). Improvements on the SCARED, which measure anxiety, ranged from 0-27 (up to 33%), and the CEER-9 scale, which indicates emotional regulation, ranged from 2-7 (22-78%). Finally, the 9-item SNAP scale measuring inattention showed improvements ranging from 2-8 points on the raw scale, which equated to 7-30%.

Notably all three patients used cannabis as an adjunct to their other medications (e.g., stimulants, antidepressants, or mood stabilizers). Patient 1 described cannabis as ‘a really good helping hand’ to compliment his other medications. Patient 2 was able to discontinue his stimulant pharmacotherapy, but acknowledged that the ‘cannabis, in addition to a change in prescription medications to lithium, helped to change his life'. Plasma levels of the cannabinoids were not detectable at trough levels suggesting that the effects of the cannabis may not be sustained throughout the day; however, the patients perceived the effects of the cannabis to last throughout the day. This bespeaks to the importance of the other medications to ensure treatment success.

All three patients discussed the use of cannabis with their psychiatrist and were authorized oral cannabidiol oil CBD:THC (20:1) from a medical source. Our patient interviews and accompanying blood levels, however, indicated that this route and formulation was not consistent and that the patients sought out a product and regimen that worked for them. Two patients reported taking cannabis once daily, whereas the other patient preferred a twice daily regimen. Two patients preferred smoking cannabis (as opposed to an edible oil). With respect to chemical composition, one patient preferred a product high in THC and low in CBD (CBD:THC 0:18-19). Another patient reported using CBD:THC 20:1, but high amounts of THC and no CBD were detected in the post-dose sample, which brings into question the contents of product used by the patient. The use of cannabis is also complicated by the dual supply streams in Canada. Two patients obtained their cannabis from a recreational cannabis store, versus a medical source due to significant cost differences (double the price for medical cannabis). Unlike other medications, patients are freely available to choose their cannabis product and source. Even within the same source, batch to batch variation is expected, which contributes to significant inter and intra-patient variability with cannabis-based medicine.

An increasing number of patients are self-medicating with cannabis for the treatment of ADHD. Yet a dearth of literature exists on this topic and only two other published case reports of patients receiving benefits from cannabis were found in the literature. One publication from 2008 reported improvement in performance tests (ART2020 and TAP) in an adult male smoking cannabis, suggesting that THC may have atypical effects in patients with ADHD [27]. A second case report in 2018 described improved symptoms in an ADHD patient who was taking a product high in THC. [28] Although the potential mechanism of cannabis remains to be determined, cannabinoids, such as THC, may mediate their effects through induction of dopamine release in the human striatum [28,29]. Elucidating such mechanisms will be particularly challenging since the biochemical composition of cannabis (e.g., phytocannabinoids, terpenes and flavonoids) varies from strain to strain. Plasma cannabinoid concentrations of two of the patients in the present discussion were high in THC (with no CBD), while the other patient had higher CBD concentrations, but THC was still present. In previous literature, products high in THC or containing both THC and CBD ameliorated ADHD symptoms [15,27,28]. While we cannot draw any conclusions on the optimal ratio of CBD:THC, we suggest that future studies involve a product consisting of some amount of THC (instead of a product consisting only of CBD).

An important limitation of case reports are their inability to generalize to a wider population given the selection bias, and there is limited information that can be gleaned from these reports of a few selected patients. While randomized controlled trials are urgently needed to provide insight on the efficacy of cannabis in the treatment of ADHD, such studies will never be performed with smoked cannabis flower and we are left to rely on observational data for these exposures. This report adds to the literature by providing detailed personal accounts from three patients and objective evidence of improvement on validated measures for ADHD symptoms. Clinicians who care for patients who self-medicate with cannabis should aim to objectively monitor symptoms, using validated scales for ADHD and other comorbidities. The patients presented in this case report were also taking concurrent medications; therefore, the added benefits of cannabis on ADHD symptoms are unclear. Significant variation noted amongst these three individuals (e.g., product, chemical composition, dose, route of administration and supplier) highlights the challenges with cannabis-based medicine development and research.

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Statement of Ethics

Written informed consent was obtained from patients for publication of the details of their medical case and ethics approval for data collection was approved the by Biomedical Research Ethics Boards at the University of Saskatchewan (#1726).

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CHAPTER 4. MEDICAL CANNABIS IN SCHOOLS; A SCOPING REVIEW

Awal M, Kelly LE, Anderson J, Brace T, Brown C, Buettner T, King PM, Klemmer J, Lougheed T, O'Shea K, Mansell H. Medical Cannabis in Schools; A Scoping Review. Cannabis Cannabinoid Res. 2022. [Accepted]

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4.1 Abstract

Objectives: An increasing number of children and youth in Canada are taking medical cannabis for complex medical conditions. While they deserve safe and consistent access to pharmacotherapy throughout the day, administrative policies on cannabis use in schools are inconsistent. A scoping review identified policies and publications associated with medical cannabis in Canadian schools.

Methods: Five databases (Scopus, PubMed, CINAHL, EMBASE, and Web of Science) were searched to identify scientific literature. Legislation in each province and territory and Ministry of Education webpages were reviewed for pertinent laws and policies regarding cannabis use in schools.

Results: The scientific search resulted in 1289 articles. The five included articles pertained to implications for school nurses in the United States, which are not relevant to the Canadian context. A search of Ministry of Education websites identified only one policy with information regarding medical cannabis in schools (from Ontario). Federal legislation (the *Cannabis Act*) does not specifically address medical cannabis in schools, and there is a lack of consistency in terminology and clarity within provincial and territorial laws. All provinces and territories prohibit smoking and vaping of cannabis on school property and some provinces prohibit any method of cannabis consumption.

Conclusion: In Canada, there is a lack of guidance for medical cannabis administration, storage, and disposal in schools, with some policies explicitly prohibiting this type of treatment. This shifts the burden to families to individually create plans school by school. A federally harmonized approach to supporting children who take cannabis for medical purposes ought to be explored.

4.2 Introduction

Many children suffer from complex medical conditions that do not respond to traditional therapies. Such conditions can dramatically affect quality of life for both the child and family [1,2]. Recent literature indicates medical cannabis is efficacious in treating chemotherapy induced nausea and vomiting, and seizure reduction in intractable epilepsy [3,4]. While research is in its infancy, there is an interest in using cannabis for neurodevelopmental and behavioural disorders such as autism spectrum disorder [5]. A growing body of evidence supports the use of medical cannabis for chronic pain, albeit most research has been performed in adults [6]. Studies indicate public support for medical cannabis is increasing, and with research evolving in this area the trend will likely continue [7,8]. In 2018, half of paediatricians and subspecialists reported managing at least one child who takes cannabis for medical purposes and nearly a quarter (22%) managed five or more [9].

In Canada, medical cannabis has been legal for two decades. The 'Medical Marihuana Access Regulations' (MMAR) program initiated in 2001 allowed for patients to obtain cannabis for federally sanctioned therapeutic purposes, provided it was authorized by a physician and the patient became registered as an authorized user [10]. The program has since undergone significant revisions, and medical cannabis is no longer limited to specific indications. Nevertheless, patients who take medical cannabis have reported a lack of support and stigmatization [11-13]. In 2015, a high school student from Saskatchewan (who was authorized cannabis for pain relief from a rare bone disease) filed a human right's case after being prohibited from smoking cannabis or attending classes while under its influence [14]. The issue of student access to cannabis at schools was also brought to a forefront in Illinois (the United States of America), when a student was not permitted to consume prescribed cannabidiol at school [15]. In response to this lawsuit, legislation was passed allowing students to access medical cannabis on school grounds [15,16]. A significant amount of public discourse has been generated about this issue in the United States. As such, other states have followed suit by examining and amending policies regarding medical cannabis in schools [15,17,18]. We are unaware of the extent to which such appraisals have taken place in Canada.

The Canadian Collaborative for Childhood Cannabinoid Therapeutics (C4T) platform was established in 2018 to generate and appraise evidence on cannabis-based therapies for children. This is a multidisciplinary team consisting of more than 101 stakeholders, including parents, health care providers, scientists, and policy makers from across Canada, united by the common goal of studying and advocating for the safe use of medical cannabis among children [19]. A Medical Cannabis in Schools working group was developed to identify gaps related to medical cannabis among children and youth in schools. This subcommittee of researchers, healthcare providers, educators, and parent advisors supports comprehensive family-centered advocacy, policy development, health promotion and dissemination of education for safe medical cannabis use in Canadian schools [20]. The Medical Cannabis in Schools working group's initial priority was to appraise currently available literature on this topic.

4.3 Methods

A scoping review using Arskey and O'Malley's scoping review framework [21] was undertaken to identify policies and publications associated with medical cannabis in Canadian schools (kindergarten and grades 1-12).

Literature search process

An electronic literature search was initially conducted between July 5, 2020 and June 17, 2021, and was updated in October 2021. The search was conducted in two phases: 1) Scientific literature search and 2) Policy review. For phase 1, five databases (Scopus, PubMed, CINAHL, EMBASE, and Web of Science) were used to identify relevant scientific literature. The search terms are shown in table 1. For phase 2, the legislation pertaining to cannabis use and consumption was identified and reviewed for each province and territory using the Google and Google scholar search engines and the Canadian Legal Information Institute (CanLII) database. The Ministry of Education webpages for each province and territory in Canada were also reviewed for pertinent policies about cannabis in schools. Relevant grey literature was searched during both phases of the search and only articles in English were assessed. We included the following in our review: Any policy pertaining to medical cannabis in schools in Canada, and any academic literature generated about medical cannabis in schools (without country exclusion).

Table 4.1. Search Strategy for Scientific Databases

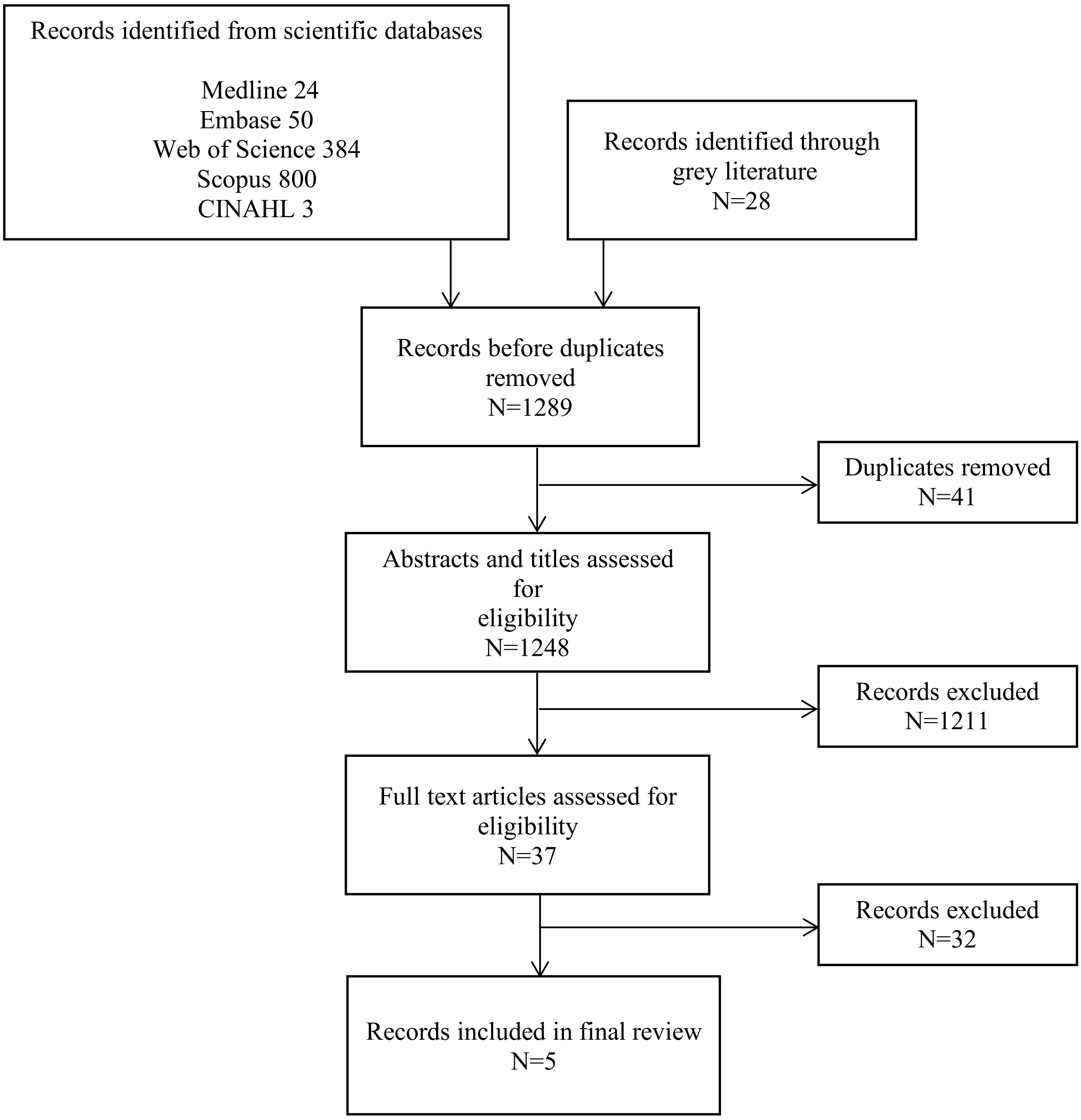
Concept	Keywords	Databases
Cannabis	medical cannabis* OR medical marijuana*	MEDLINE, EMBASE, SCOPUS, CINAHL, and Web of Science
Policy	Laws* OR legislation* OR policy*	
School	School* OR school board* OR ministry of Education*	

Data extraction

Phase 1 – Scientific Literature Search

The search resulted in 1289 articles, which were added to EndNote (Clarivate Analytics). After the duplicates were removed (n=41), two individuals screened the abstract and/or introduction of the articles to determine inclusion status and discussed any potential discrepancies. After reviewing the full text of 37 publications, 5 met our inclusion criteria. Figure 1 illustrates the literature search and screening process.

Figure 4.1. PRISMA-style flow diagram of the scientific article selection process



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Phase 2 – Policy Review

To extract information from specific school policies, a data collection form was created by the Medical Cannabis in Schools working group and was reviewed by the broader

C4T research platform during a monthly meeting for discussion and feedback. The data extraction form was designed to capture specific information about the document's content [*purpose (directive vs educational), policy specific to cannabis (yes/no), inclusion of medical and/or recreational cannabis (yes/no), definition of medical use, permitted (or unpermitted) routes of cannabis ingestion, medical authorization requirement (yes/no), and other requirements (e.g. documentation, diagnosis administration, education, caregiver, storage and/or disposal requirements)];* as well as the publisher and location. The data was collated electronically using Microsoft Excel software (Microsoft Corporation, Seattle, USA).

4.4 Results

Phase 1 – Scientific Literature Search

Five manuscripts were identified during the scientific literature search, all of which pertain to cannabis policy and implications for school nurses in the United States [22-26]. These articles describe the contradictory legislation between the states where medical cannabis is legalized, and Federal law under which it is designated as an illegal substance. As such, it is the position of National Academy of School Nurses (NASN) that only FDA approved cannabis/marijuana medications be allowed in the school setting. (A summary of these articles is found in table 4.2).

Table 4.2 Summary of the academic literature identified in the search

Name	Author	Date	Location	Type of Article	Article overview	Reference
Medicinal Use of Marijuana: What School Nurses Need to Know	DeWitt-Parker C.	May 2016	USA	Review/ guidance document	Cannabis for students and persons with developmental disabilities were legalized in New Jersey and this article provides a frame of reference for school nurses to encourage awareness of the implications for student health and relevant nursing interventions in the school setting.	NASN Sch Nurse. 2016;3:170-6. doi: 10.1177/1942602X 16638815. Epub 2016 Apr 1.
The NCSBN national nursing guidelines for	NCSBN	2018	USA	Guideline	A review of literature, legislation, nursing implications and guidelines for the care of the patient using medical cannabis and	[NCSBN] J Nurs Regul;2018:9;S1-60

medical marijuana					education in nursing programs.	
Position Brief - Cannabis/ Marijuana	NASN (Silver Spring, MD)	2019	USA	Position brief	Due to the contradiction between federal and state laws, it is the position of NASN that only FDA approved cannabis/marijuana medications be allowed in the school setting.	NASN. 2019. *Cannabis/Marijuana* (Position Brief). www.nasn.org/nasn/advocacy/professional- practice-documents/position briefs/ pb-cannabis
Medical Marijuana Guidelines for Practice: Health Policy Implications	Russell K, Cahill M, Duderstadt KG	Nov - Dec 2019	USA	Review/ guidance document	A review on the endocannabinoid system, legislation on medical marijuana, policy considerations, recent FDA approval of a cannabis products, nursing guidelines and implications for nursing practice.	J Pediatr Health Care. 2019;33:722-726. doi: 10.1016/j.pedhc.2019.07.010.
Medical Cannabis and School Separating Fact from Fiction	NASN (Tapper Strawhacker, MT)	Jan 2020	USA	Review/ guidance document	While most US states have legalized medical cannabis, it is still designated as an illegal substance under US Federal law (Schedule 1). This is a guidance document for school nurses who encounter a student treated with medical cannabis.	NASN Sch Nurse. 2020;35:43-48. doi: 10.1177/1942602X19877561. Epub 2019 Oct 29.

NASN: National Association of School Nurses; NCSBN: National Council of State Boards of Nursing

Phase 2 – Policy Review

There is a complex web of federal and provincial/territorial laws that govern the use of cannabis in Canada. Generally speaking, the *Cannabis Act* and *Cannabis Regulations* are the federal legislation which decriminalized non-medical or recreational cannabis possession, cultivation and consumption for adults [27,28]. The *Cannabis Regulations* replaced the former Access to Cannabis for Medical Purposes (ACMPR) [28]. Part 14 of the *Cannabis Regulations* provides access to cannabis for medical purposes and specifically provides access to medical cannabis by young persons. Part 14 does not place any age restrictions on “young persons”, is silent on how young persons may consume or use medical cannabis and where they may consume it.

Under the *Cannabis Act* each province and territory has the power to set its own rules for details such as the distribution and sale of recreational cannabis and where public consumption of cannabis may take place. For the most part provincial and territorial governments have not imposed additional limits or restrictions on the use of medical cannabis, except some jurisdictions have imposed limits on where cannabis, including medical cannabis, can be consumed. The provincial and territorial legislation governing cannabis are presented in Table 4.3. In some documents, "cannabis" refers only to recreational cannabis (e.g. ON), whereas in others it does not specify (e.g. SK) or references both cannabis for both medical and recreational purposes (e.g. BC), making interpretation of the various laws and policies challenging. While Nova Scotia refers to "medical-use cannabis as "cannabis used for medical purposes", Newfoundland/Labrador defines a "medical cannabis user" as a "person authorized to possess cannabis for the person's own medical purposes in accordance with the federal Act", and several policies do not provide a clear definition for medical cannabis.

Table 4.3. Provincial/territorial legislation for cannabis consumption

Province/ Territory	**Provincial cannabis legislation around possession and consumption**	**Relevant Policies**
Alberta (AB)	The Alberta Cannabis Framework	An Act to Control and Regulate Cannabis, SA 2017, c 21, Available from: https://canlii.ca/t/53233. Accessed 10/22/2021
British Columbia (BC)	Cannabis Control and Licensing Act	Cannabis Control and Licensing Act, SBC 2018, c 29, Available from: https://canlii.ca/t/554rh. Accessed 10/22/2021
Manitoba (MB)	The Safe and Responsible Retailing of Cannabis Act	The Safe and Responsible Retailing of Cannabis Act (Liquor and Gaming Control Act and Manitoba Liquor and Lotteries Corporation Act Amended), SM 2018, c 9, Available from: https://canlii.ca/t/54r96. Accessed 10/22/2021 The Smoking and Vapour Products Control Act, C.C.S.M. c. S150, Available from: https://web2.gov.mb.ca/laws/statutes/ccsm/_pdf.php?cap=s150. 10/22/2021
New Brunswick (NB)	Cannabis Control Act Cannabis Management Corporation Act Cannabis Education and Awareness Fund Act	Cannabis Control Act, SNB 2018, c 2, Available from: https://canlii.ca/t/5393h. Accessed 10/23/2021 Cannabis Education and Awareness Fund Act, SNB 2018, c 4, Available from: https://canlii.ca/t/544ts. Accessed 10/23/2021 Cannabis Management Corporation Act, SNB 2018, c 3, Available from: https://canlii.ca/t/54vxr. Accessed 10/23/2021

		Smoke-free Places Act, RSNB 2011, c 222, Available from: https://canlii.ca/t/53l69. Accessed 10/23/2021
Newfoundland and Labrador (NL)	Newfoundland and Labrador Cannabis Control Regulations	Cannabis Control Act, SNL 2018, c C-4.1, Available from: https://canlii.ca/t/54c0r. Accessed 10/22/2021 Smoke-free Environment Act, 2005, SNL 2005, c S-16.2, Available from: https://canlii.ca/t/53gdz. Accessed 10/22/2021
Nova Scotia (NS)	Cannabis Control Act	Cannabis Control Act. 2018, c. 3, s. 1, Available from: https://nslegislature.ca/sites/default/files/legc/statutes/cannabis%20control.pdf. Accessed 10/22/2021 Smoke-free Places Act, SNS 2002, c12, Available from: https://canlii.ca/t/54bpr. Accessed 10/22/2021
Northwest Territories (NWT)	Cannabis Legalization and Regulation Implementation Act	Legislative Assembly of the Northwest Territories. Cannabis Legalization and Regulation Implementation Act. Bill 6, Available from: https://www.ntassembly.ca/sites/assembly/files/bill_6_0_0.pdf Accessed 10/22/2021 Cannabis Smoking Control Regulations, NWT Reg 133-2018, Available from: https://canlii.ca/t/53gdg. Accessed 10/22/2021
Nunavut (NV)	Cannabis Act Cannabis Statutes Amendment Act	Cannabis Act, SNu 2018, c 7, Available from: https://www.nunavutlegislation.ca/en/statutes-of-nunavut/2018. Accessed 10/22/2021 Cannabis Statutes Amendment Act, 2018, c.8, Available from: https://www.nunavutlegislation.ca/en/statutes-of-nunavut/2018. Accessed 10/22/2021
Ontario (ON)	Cannabis Control Act	Cannabis Control Act, 2017, S.O. 2017, c. 26, Sched. 1. Available from: https://www.ontario.ca/laws/statute/17c26?search=Cannabis+Control+Act%2C+2017%2C+S.O.+2017%2C+c.+26%2C+Sched.+1. Accessed 10/23/2021 Smoke-Free Ontario Act, 2017, SO 2017, c 26, Sch 3, Available from: https://canlii.ca/t/53m3f. Accessed 10/23/2021
Prince Edward Island (PEI)	Cannabis Control Act	Cannabis Control Act, RSPEI 1988, c C-1.2, Available from: https://canlii.ca/t/53gfr. Accessed 10/23/2021 Smoke-free Places Act, RSPEI 1988, c S-4.2, Available from: https://canlii.ca/t/538zc. Accessed 10/23/2021
Quebec (QB)	Cannabis Regulation Act An Act to tighten the regulation of cannabis	Cannabis Regulation Act, CQLR c C-5.3, Available from: https://canlii.ca/t/54vhp. Accessed 10/23/2021 An Act to tighten the regulation of cannabis, SQ 2019, c 21, Available from: https://canlii.ca/t/5375l. Accessed 10/23/2021
Saskatchewan (SK)	The Cannabis Control (Saskatchewan) Regulations	The Cannabis Control (Saskatchewan) Regulations, RRS c C-2.111 Reg 1, Available from: https://canlii.ca/t/54b3d. Accessed 10/22/2021
Yukon (YT)	The Cannabis Control and Regulation Act	Cannabis Control and Regulation General Regulation, SY 2018, c.4, Available at: https://laws.yukon.ca/cms/images/LEGISLATION/PRINCIPAL/2018/2018-0004/2018-0004.pdf Accessed 10/23/2021

		Tobacco and Vaping Products Control and Regulation Act, SY 2019, c14, Available from: https://canlii.ca/t/549bl. Accessed 10/23/2021

All provinces and territories indicate that smoking and vaping of cannabis is prohibited on school property. In some cases this is explicitly stated in the provincial/territorial cannabis laws, whereas in others it is specified in an amendment to the legislation regarding smoking and vaping. Exceptions are generally not provided for medical cannabis. Some provinces are even more restrictive and prohibit any method of cannabis consumption on a school campus (e.g. BC).

The ministry of education web pages were identified for all provinces and territories and searched for policies and documents pertaining to medical cannabis. Table 4.4 indicates the province and territory's respective population, the ministry's school structure/organization and website [29-40]. While many documents indicate cannabis is prohibited on school property, most documents are vague or do not address medical cannabis. We found two directives from Alberta acknowledging that medical cannabis is permissible [41,42]. The most comprehensive document, published in Ontario, was educational in nature and intended to provide clarity to schools and school boards around the provincial/territorial legislation with regards to medical and recreational cannabis [43] (table 4.5).

Table 4.4 Ministry of Education websites reviewed

Province/ Territory	Population*	Ministry's school structure/organization*	Website
Alberta (AB)	4,442,879	42 public school authorities (1,564 schools) 159 private school authorities (207 schools) 13 charter school authorities (24 schools) 4 francophone school authorities (43 schools) 17 separate school authorities (423 schools) 14 charter school authorities (26 schools) 42 provincial school authorities (1564 schools)	https://www.alberta.ca/education.aspx
British Columbia (BC)	5,214,805	60 school districts 1578 public schools 364 independent schools	https://www2.gov.bc.ca/gov/content/governments/organizational-structure/ministries-

			organizations/ministries/education.
Manitoba (MB)	1,383,765	5 school divisions 38 school districts 2389 schools	https://www.edu.gov.mb.ca.
New Brunswick (NB)	789,225	7 school districts 320 schools	https://www2.gnb.ca/content/gnb/en/departments/education.html.
Newfoundland and Labrador (NL)	520,553	2 school boards 260 public schools 7 private schools 3 First Nations schools	https://www.gov.nl.ca/education/.
Nova Scotia (NS)	992,055	8 school districts 374 public schools More than 16 private schools	https://beta.novascotia.ca/government/education-and-early-childhood-development.
Northwest Territories (NWT)	45,504	8 education authorities 49 schools	https://www.ece.gov.nt.ca/en
Nunavut (NV)	39,403	6 district education authorities 44 public schools	https://www.gov.nu.ca/school-information
Ontario (ON)	14,826,276	73 public school boards 10 school authorities (4 geographically isolated boards and 6 hospital-based school authorities) 4844 schools 1573 public schools	https://www.ontario.ca/page/ministry-education
Prince Edward Island (PEI)	164,318	2 school districts 62 public schools 5 private schools	https://www.princeedwardisland.ca/en/topic/education-and-lifelong-learning
Quebec (QB)	8,604,495	72 school centers and school boards (60 French, 1 special-status service centers & 9 English, 2 special-status school boards) More than 2700 public educational institutions 257 private schools	http://www.education.gouv.qc.ca/en/home/
Saskatchewan (SK)	1,179,844	27 school divisions 63 independent schools	https://www.saskatchewan.ca/government/government-structure/ministries/education
Yukon (YT)	42,986	28 schools	https://yukon.ca/en/department-education

*Data for this table was obtained from the Ministry Websites (indicated in the table) as well as the following references: (Statistics Canada 2021 [29]; Alberta Education 2021[30]; British Columbia 2019 [31]; British Columbia 2021 [32]; Manitoba 2019/2021 [33]; New Brunswick Canada 2018 [34]; Newfoundland and Labrador Canada Education 2019/20 [35]; Nova Scotia 2020 [36]; Teach in Nova Scotia 2021 [37]; Ontario Ministry of Education 2021[38]; Ontario 2021 [39]; Quebec 2021 [40])

Table 4.5. Medical cannabis policy-related publications generated from search

Name	Publisher (Author)	Date	Location	Type of publication	Purpose	Specific to only cannabis	Article overview	Reference
Cannabis information for schools and school boards [43]	Queen's Printer for Ontario	Fall 2019	ON	Fact sheet	Educational	yes	fact sheet about recreational and medical cannabis in schools	ISBN 978-1-4868-2918-7 (Print) ISBN 978-1-4868-2919-4 (PDF) http://www.edu.gov.on.ca/eng/healthyschools/cannabis-fact-sheet-en.pdf Accessed: 10/23/2021
EM.BP. Alcohol Tobacco and Cannabis on and in Division Property at Division Functions [41]	Edmonton Public Schools	Jan 28, 2020	Edmon-ton, AB	Board Policy	Directive	no	purpose is to establish expectations regarding alcohol, tobacco, and cannabis	Edmonton Public Schools. EM.BP. https://epsb.ca/ourdistrict/policy/e/em-bp/EM.BPAlcoholicBeveragesandCannabis.pdf Accessed: 10/23/2021
Administrative Regulation No. 6002 [42]	Calgary Board of Education	Sept 21, 2020	Calgary, AB	Administrative regulation	Directive	no	guidelines for supporting students with health concerns	Calgary Board of Education. AR 6002, Student Health Services https://cbe.ab.ca/GovernancePolicies/AR6002.pdf Accessed: 10/23/2021

4.5 Discussion

As the use of medical cannabis in children increases, an understanding of the current landscape is essential for supporting evidence-informed decision making and policy development in all Canadian schools. The current federal legislation in Canada (the *Cannabis Act* and *Cannabis Regulations*) does not address medical cannabis for children in schools; furthermore, there is a lack of consistency in terminology and clarity within the provincial and territorial laws. We also discovered a lack of school policies to support families and educators in administering cannabis for medical purposes to a child at school. Only one educational publication (from the government of Ontario directed to schools and school boards) provided clear information about both medical and recreational cannabis in schools [43]. None of the documents provided specific routine information (such as requirements around administration, documentation, storage and/or disposal requirements) that were identified by C4T members as key areas for school policies a priori.

Our search of the medical literature in five scientific databases generated only five articles, indicating that research in this area is in its infancy. All articles identified provided guidance to school nurses in the United States faced with conflicting state and federal laws about cannabis use in schools. Interestingly, it is the position of NASN that only FDA approved cannabis medications be allowed in the school setting [24]. In the Canadian context, where medical cannabis is legal both federally and provincially/territorially, and a purified cannabidiol oral solution (Epidiolex®) is not commercially available as it is in the US, this recommendation is not relevant. NASN also recommends that school nurses help to lay the foundation for safe care of patients using medical cannabis and recreational cannabis, and outlines several competencies for school nurses. These include a comprehensive familiarity with the legislation, an understanding of the endocannabinoid system, cannabis pharmacology, and associated research, as well as considerations for the safe use of cannabis in a school setting [23]. While these goals are idealistic, most schools in Canada do not have access to a nurse. This potentially places the responsibility of medical cannabis-related activities (e.g. administration, monitoring for adverse events, product storage and disposal) on educators or school administrators. Given that many healthcare providers lack the knowledge and confidence necessary to support medical cannabis [44,45], it is unreasonable to place these expectations on teachers, without provision of additional education, training, or support. Furthermore, guardians or caregivers should not be expected to be responsible for providing/administering medical cannabis to their children while in school. Procedures must be developed to provide guidance on administration, storage, disposal, monitoring, and training to support schools and students who require medical cannabis while at school.

Medical cannabis must be treated like any other medication; children and youth ought to have the right to access it as part of their medical treatment plan while at school. Cannabis has a complex history among Canadians as a previously illicit substance with a newly legalized recreational market; however, cannabis as a medicine continues to be stigmatized particularly with regards to therapeutic uses for children and youth [12]. In our review of cannabis legislation, we found all provinces and territories prohibit smoking and vaping of cannabis on school property and some provinces prohibit any method of cannabis consumption on school property. The preferred dosage form for cannabis-based medicine in pediatrics is oral. However, in some circumstances exceptions may apply [14].

Canadian courts have a history of using the Canadian Charter of Rights to strike down laws that limit access to medical cannabis. In 2000, the Ontario Court of Appeal in R. v. Parker ruled that persons with a medical need had the right to possess marijuana for medical purposes [46]. In 2015, in R. v. Smith, the Supreme Court of Canada determined that restricting access to only dried marijuana for medical purposes was unconstitutional and that persons with a medical need had the right to access and use other cannabis products [47]. The Supreme Court of Canada, in the Adler case, found that while providing medical service does not look like an educational service, school districts may have to provide such service to ensure “that children with special needs have full access to the public school system” [48]. It is possible that provincial or territorial laws that prohibit or limit access to medical cannabis at schools will be subject to a Charter challenge. Whether a restriction on vaping or smoking medical cannabis in school will be seen as a reasonable limit on a child’s access to medical cannabis will be determined on the facts of the case and the child’s specific circumstances. In light of the broad protection Canadian courts have given access to medical cannabis, it is unlikely that an absolute prohibition on access to any form of medical cannabis in school would withstand Charter scrutiny.

Several limitations of this study warrant consideration. First, this scoping review was indeed limited by the availability and quality of literature available on this topic. Given the scarcity of information, we opted to review any relevant scientific literature, which resulted in the inclusion of review articles on the topic rather than studies. Secondly, all data in this paper wereas available publicly and we did not contact school boards or provincial/territorial authorities. As such, we were not privy to institutional specific policies that could potentially have been disseminated by schools directly to parents, and our search conducted primarily through the ministry of education webpages may have missed some local documents. This review was limited to publications in English and it is possible that relevant literature in other languages (particularly French) was missed. Putting the information into context is somewhat challenging, since there is no national or provincial/territorial reporting structure to provide data on the number of school-aged children taking medical cannabis in Canada or to the extent to which it is used in schools. Despite these limitations, this paper is the first to review policies on medical cannabis in schools and identifies several key gaps which deserve attention which will guide the Medical Cannabis in Schools working group.

4.6 Conclusion

Children and youth with medical conditions require knowledgeable and unbiased caregivers and educators who can support their treatment plan. This scoping review highlights a lack of published guidance to support families and educators navigating the use of medical cannabis in schools. Federal guidelines recommending a harmonized approach to the administration, storage, and disposal of medical cannabis for children is needed.

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CHAPTER 5. MEDICAL CANNABIS IN SCHOOLS: A QUALITATIVE STUDY ON THE EXPERIENCES OF CLINICIANS

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5.1 Abstract

Objectives: Guidance is lacking for medical cannabis use in Canadian schools in both legislation and approach; the impact of ambiguous policy on patient care is unknown. A qualitative study was undertaken to explore the experiences of clinicians who care for school-aged children who take medical cannabis.

Methods: Semi-structured interviews were recorded and transcribed verbatim. Qualitative content analysis was performed using Dedoose qualitative software. Meaning units and codes were obtainted from the transcripts, which were further consolidated into categories and subcategories.

Results: Thirteen physicians were interviewed virtually, representing 7 provinces in Canada. The physicians provided care for between 5 and hundreds of school-aged children who took medical cannabis. The most common indications were refractory seizure disorders and autism. The interviews provided rich descriptions on perceptions of medical cannabis in schools, and in general. Five overarching categories were identified across both domains including variability, challenges (subcategories: lack of knowledge, stigma, lack of policy and pragmatic challenges), potential solutions (subcategories: treat it like other medications, communication, education, and family support), positive experiences and improvements over time.

Conclusion: In Canada, cannabis-based medicine use in schools still faces important challenges. Effective education, communication, family support and policy refinements that allow cannabis to be treated like other prescription medications are recommended to improve the status quo. These findings will guide the C4T Medical Cannabis in Schools Working Group's future priorities and initiatives.

5.2 Introduction

The reported use of medical cannabis has increased in recent years, in part, stimulated by media attention and case reports of treatment success in some conditions [1-3]. Although the evidence-based literature for cannabis use in children is limited, a growing number of clinicians are authorizing it for specific indications. The most robust data is in drug-resistant epilepsy, where four randomized controlled trials and several non-randomized studies report significant reductions in seizures [4]. Other therapeutic areas in children include chemotherapy-induced nausea and vomiting, chronic pain, and autism spectrum disorder [5,6]. The 2016 Canadian Pediatric Society (CPS)'s official position statement indicates that using cannabis for medical purposes in children should be evaluated on a case-by-case basis; only by clinicians with condition-specific expertise, and always a comprehensive discussion of potential benefits and risks [7]. Cannabis for the treatment of epilepsy in children should also be evaluated long-term, using well-designed research into developmental effects [7]. A recent survey of paediatricians (Canadian Paediatric Surveillance Program (CPSP) (n=877)) indicated half of all respondents have encountered patients who used cannabis for medical purposes in the previous year [8].

In 2018, Canada became the second country to federally legalize both medical and recreational cannabis creating a dual supply chain [9]. Under the *Cannabis Act*, patients may obtain cannabis for medical purposes from a licensed producer with medical authorization from a clinician. In contrast, cannabis for recreational use can be obtained without medical authorization by adults, from retail stores or grown at home. Each province or territory can further regulate how cannabis can be sold and consumed. Except for two pharmaceutical grade products, Sativex® (nabiximols) [10] and Cesamet® (nabilone) [11], cannabis does not go through Health Canada's drug review and approval process or have a Drug Identification Number (DIN) [12]. As such, caregivers of children who require medical cannabis and clinicians have reported barriers, including difficulties with access, cost, or stigma [2,13,14]. Anecdotally, some physicians reported barriers to having medical cannabis administered in schools, although these personal accounts are not substantiated by research.

The Canadian Collaborative for Childhood Cannabinoid Therapeutics (C4T) is an academic-led team of parents, doctors, pharmacists, youth, nurses and scientists studying medical cannabis use by children [15]. The C4T "Medical Cannabis in Schools" working group [16] recently performed a scoping review to identify policies and publications associated with medical cannabis in Canadian schools [17]. The review highlights a lack of guidance and clarity, with some legislation prohibiting the use of cannabis in schools. The extent to which these policies (or lack thereof) have impacted patient care remains unknown. This study aimed to learn about the experiences of clinicians providing care for school-aged children who require medical cannabis.

5.3 Methods

Population of interest and recruitment

The methodology used was qualitative description, which aims to explore a phenomenon of interest using participants in a particular situation [18,19]. Clinicians who authorize or provide care for school-aged children and youth were recruited by way of a study invitation shared through websites and social medical channels expected to reach the target audience (e.g., the C4T and the Canadian Consortium for the Investigation of Cannabinoids (CCIC)). As well, members of these networks were encouraged to share recruitment materials, which linked to an online survey for potential participants to provide their contact information.

Data Collection

Clinicians who participated were provided an option of a virtual (Cisco Webex) or telephone interview, which used a semi-structured interview guide (table 5.1). The guide was created by the Medical Cannabis in Schools working group (parents of children who take medical cannabis, physicians, community health nurses, and a pharmacist, n=10), and further reviewed by an external qualitative researcher. In the absence of previous literature, the questions were inductive and designed to elicit responses on the experiences, including facilitators and/or challenges. Self-reported demographic data (province, clinician specialty, practice, sex/gender, and ethnicity) was collected. The recorded interviews were conducted by H.M., a researcher with experience in qualitative methodology, and continued until the topic was thoroughly discussed and the participant had nothing more to add. A $25 gift card was offered to the participants. The local Behavioural Ethics Board approved the study (Beh#2804), following best practice guidelines for undertaking qualitative research [20,21].

Table 5.1 Semi-structured interview guide for clinicians

Introductory Questions	Tell me about your relationship to the child(ren)/youth that is (are) using medical cannabis in schools?
	Describe the situation for which the child/youth is (are) using medical cannabis in schools?
Exploratory Questions	Describe your patient's experience with using medical cannabis in schools?
	What (if any) are the requirements for your patient(s) to use their medical cannabis at school?
	What was easy or difficult for your patient(s) about using medical cannabis in schools?
	What was easy or difficult for you as clinician using medical cannabis in schools?
	How well-informed do (or did) you feel the school was about medical cannabis for children/youth?
	What information do you think is important to know for teachers or school administrators to know about medical cannabis for children/youth?
	What skills do you feel a parent/caregiver requires to navigate medical cannabis in schools?
	Are there any supports that you benefited from? Are there any supports that weren't available that you could have benefited from? If so, please describe.
	If you had to tell another clinician or parent how to navigate medical cannabis in schools, what would be the key things important for them to know?
Exit Question	What else do you want me to know about your experience with medical cannabis for children/youth in general?

Data analysis

The interviews were transcribed verbatim by the Canadian Hub for Applied and Social Research (CHASR) and analyzed by two researchers experienced in qualitative analysis (HM and ZZ) using Dedoose software [22]. Qualitative content analysis was chosen as the analytical approach, since the intent was to preserve the descriptive accounts of the participants closely aligning with the manifest, rather than analyzing the latent content for underlying meaning [23]. In the first stage of the process (preparation), transcripts were reviewed thoroughly and meaning units were ascribed into sentences and statements [24]. The second stage (organization) involved the process of abstraction, and open coding was used to label meaning units. The codes were organized according to categories and sub-categories iteratively throughout the analysis. The researchers collaborated throughout this process, meeting regularly to discuss code and category relabelling and refinement. The report produced during the last phase of the research was sent to the participants for an opportunity to provide feedback.

5.4 Results

Thirteen physicians from 7 provinces took part in the study between August-November 2021. Eleven interviews were conducted by video conference and two by phone; the interviews lasted between 15 and 51 minutes. Participants ranged in age between 35 and 67, and the most cited reasons for prescribing medical cannabis were seizure disorders and autism. Some, but not all physicians, authorized CBD-only products. (Table 5.2).

Table 5.2 Self-reported characteristics of study participants

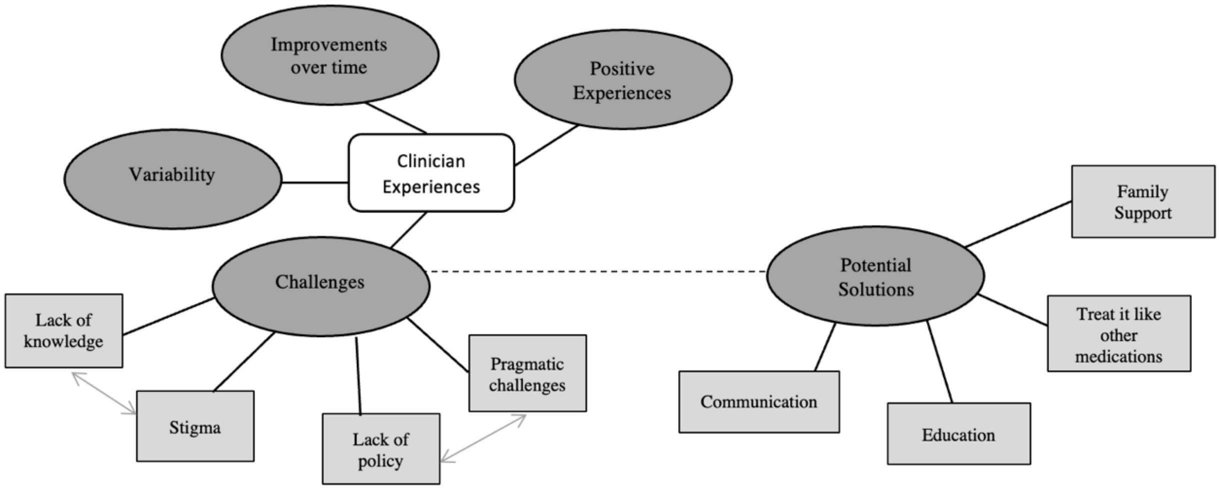
Characteristic	Number (%)
Age	
30-39	3 (23.1%)
40-49	3 (23.1%)
50-59	4 (30.8%)
60-69	3 (23.1%)
Sex and Gender	
Male	9 (69.2%)
Female	4 (30.8%)
Province of residence	
British Columbia	3 (23.1%)
Alberta	1 (7.7%)
Saskatchewan	1 (7.7%)
Manitoba	1 (7.7%)
Ontario	5 (38.5%)
New Brunswick	1 (7.7%)
Nova Scotia	1 (7.7%)
Specialty	
Pediatric neurologist	3 (23.1%)

General practitioner/ family physician	5 (38.5%)
Internist	1 (7.7%)
Pediatrician	2 (15.4%)
Pediatric psychiatrist	2 (15.4%)
Race	
Caucasian	9 (69.2%)
Caucasian (Central Eastern)	1 (7.7%)
Latin American	1 (7.7%)
Jewish	1 (7.7%)
Metis	1 (7.7%)
Estimated number of children receiving authorization for medical	
cannabis	3 (23.1%)
5-15	4 (30.7%)
20-45	6 (46.2%)
100 +	
Indications*	
Treatment resistant seizure disorders	10 (76.9%)
Autism	10 (76.9%)
Other treatment resistant behavioural or mental health disorders	10 (76.9%)
Chronic pain, palliative care, cancer	3 (23.1%)
Other	2 (15.4%)
Experience dealing with schools	
None (doses exclusively around school hours)	3 (23.1%)
Limited (between one and a few encounters)	5 (38.5%)
Several (many encounters)	5 (38.5%)

*Percentage will not add up to 100 since some participants stated more than one answer

Clinicians varied in their encounters with schools, depending on authorizing approach. Some physicians had several patients who required medical cannabis during the school day, whereas others scheduled the dose around school hours (e.g., twice daily). The interviews provided rich descriptions on perceptions of medical cannabis a) in schools and b) in general, and the results are reported according to these two domains. Figure 5.1 displays the overarching categories and subcategories. Table 5.3 provides additional supporting quotes.

Figure 5.1 Overview of categories and subcategories pertaining to clinician perceptions with medical cannabis at schools



1. Variability

Some clinicians had very few encounters with the schools, whereas others had many. Some reported positive experiences collaborating with teachers and administrators, while others reported barriers and challenges. School structure, policy, and logistics lacked consistency across the jurisdictions. Even within the same district, physicians acknowledged each situation was school dependent. Participant 9 said, "*We rely on what the parents tell us each time. And it's always something different*." As described by participant 1, "*One school refused to give cannabis oil to an eight-year-old and they had the 12-year-old sister come down to the office to administer the afternoon dose… So, it ranges from support, to complete lack of support*."

2. Challenges

Challenges with accessing medical cannabis in schools and with cannabis in general were reported and are sub-categorized as 'lack of knowledge', 'stigma', 'lack of policy' and 'pragmatic challenges.'

Lack of knowledge

Lack of knowledge about medical cannabis was perceived to be prevalent within schools, the general public, and even the medical system. Participant 7: "*There's a lot of misunderstanding about the different cannabis products, the different ingredients, as well as the dosing. So, for the vast majority, it's not well understood."* Participants commented on misconceptions, such as cannabidiol oil being intoxicating, rampant misinformation on the internet, and the knowledge gap with other healthcare providers. Participant 1: *"It used to, but doesn't anymore surprise me, how little healthcare professionals know about cannabis."*

Stigma

Some clinicians indicated stigma was not an issue, while others citied it as a barrier in their patient's medical treatment. Some participants described the impact of stigma from the school, community, or family.

> Participant 7: *"Sometimes my patients feel like they were really discriminated against and that can emotionally affect them. And that can be really frustrating as a clinician. Because I am trying to encourage a medicine, and I have people who don't have medical training or expertise or knowledge protecting their own biases on it, which could indirectly affect my patient and their health."*

Many clinicians acknowledged stigma exists within the medical profession, and some faced barriers such as prohibitive policies regarding cannabis authorization within their institution. Participant 10 said, *"I think there's still a stigma around it and in the medical profession… But hopefully with time, that is slowly getting better."* Others attributed stigma within the medical profession to the lack of randomized controlled trials. Participant 6 noted this is ironic, since many other medications are used off-label in pediatrics without scrutiny.

Lack of policy

Lack of policies for medical cannabis in schools was perceived to be challenging for teachers, administrators, patients, and physicians. According to participant 12, *"It's up to the director or principal of that school to decide how to proceed."* Some physicians described situations where cannabis was prohibited in the schools. Provisions had to be made, such as extending the dosing interval, or having the parent visit the school daily to administer the dose. These situations, while rare, cause significant challenges for the family. According to participant 1: *They [the experiences with schools] tend to be more toward neutral or positive… But the problem is, those negative situations really highlight the difficulties… patients have to kind of skirt around the regulations or rules that are in that institution."*

Pragmatic challenges

Pragmatic challenges were identified with medical cannabis administration. These included availability of a responsible person for administration during the school day, safe and secure storage of medical cannabis, and extra paperwork. Other challenges, which did not pertain specifically to schools, include its prohibitive cost, issues with obtaining a consistent product from a reputable supplier, challenges with the dosage form, and the lack of compensation for extra physician time. According to participant 8, *"I've got a couple of kids who tried it. It worked really well, but their parents can't afford it."*

3. Potential solutions

Clinicians offered insights on addressing the challenges.

Treat it like other medications

Clinicians unanimously agreed medical cannabis ought to be treated like any other medication within the school system and in general. Some lamented over the difference in regulations with cannabis (e.g., lack of DIN) and indicated that problems would be solved if regulators, the medical system, and the cannabis industry were required to treat cannabis like a normal medication. Participant 10*: "Consistency, availability, are the two biggest things… if the medical cannabis industry wants to be considered like a drug company, like a pharmacy – they need to set themselves the same standards."*

Communication

Communication between parents and teachers and the medical team was perceived to be essential for navigating medical cannabis in schools. Participants discussed the importance of both verbal and written communication for identification of barriers, solutions, and processes.

Education

Education was perceived to be an important strategy for solving challenges and decreasing stigma. Some participants indicated that standardized education for teachers and administrators would be of benefit and offered insights on the nature of such education (table 5.4).

Table 5.3 Information about medical cannabis that participants deemed 'important for schools to know'

Important principles for cannabis education	- Educate both teachers and school administrators about cannabis-based medicine due to a general lack of knowledge about this topic - Education may help to decrease stigma and improve processes - Education in schools for children should focus on recreational and medical cannabis. - Introduce medical cannabis education at a younger age to decrease stigma - The right people should educate about cannabis education (e.g., clinicians who authorize cannabis to children and are knowledgeable in the area)
Important information for teachers and school administrators	- What cannabis is - How cannabis works - Where cannabis comes from - Basic education about cannabinoids and the endocannabinoid system - The different cannabis products with their different chemical compositions and therapeutic qualities - The basic differences between THC and CBD - The abuse potential of medical cannabis is very low - What cannabis is used for medically - The process of medical cannabis authorization

	- Practical management tips such as when and how to give cannabis medically for a child - Potential side effects of cannabis and how to monitor for them and manage them - Signs of intoxication - How to safely store cannabis

Support for families

Participants emphasized that families require support to navigate medical cannabis in schools and in general. A knowledgeable practitioner, who is willing to take the time to educate, provide support, and advocate on behalf of the patient was considered important by all, and a referral to a clinic or practitioner who specializes in cannabis medicine was cited by some. Peer to peer support was also mentioned as a valuable resource.

4. Positive experiences

Despite the variability in experiences, several participants described positive encounters with schools. According to participant 10: *"I think there are schools that have been very accepting of it [medical cannabis]"* and participant 1: *"Many schools are supportive."* Some clinicians also commented on the effectiveness of cannabis-based medicine in their practice. Participant 10: "*I think there's so much more to learn, but what is clear is that some children really benefit from this therapy and that we shouldn't let stigma or biases prevent the kids from getting that benefit*."

5. Improvements over time

Nearly all participants (12/13) described how significant improvements have occurred both in school-related experiences, and in those related to cannabis in general. Clinicians described advancements in knowledge and acceptance of cannabis medicine, and improvements in policies, practices, and stigma.

> Participant 6: *"I've been doing it for a while [authorizing cannabis] and it was like a salmon swimming upstream for years and years and years across all sorts*

of dynamics. My colleagues, the nursing association, the long-term care facilities. Now, it's so much less resistance and I would put schools in there as well."

Some participants acknowledged that there is still room to grow. Participant 4, "*I would say it has gotten better. But it's still not where it needs to be."*

5.5 Discussion

We interviewed 13 clinicians across Canada and their experiences with cannabis-based medicine in schools varied. Some described encounters where schools had refused to administer medical cannabis, while others highlighted a positive collaboration with educators. No consistent pattern was observed with respect to location (province or city), or type of school, and the participants confirmed that each situation was unique.

Despite mixed experiences, participants shared several similarities. All clinicians authorized medical cannabis for children, and some managed patients who were referred specifically for cannabis expertise. Participants described significant benefits with cannabis-based medicine but acknowledged that the primary role of cannabis is in refractory conditions. Throughout the dialogue it was evident that these participants acted as tireless advocates for their patients. Remarkably similar perceptions were illustrated in the subcategories of lack of knowledge, stigma, lack of policy, and pragmatic challenges. Interestingly, these subcategories may be interconnected. Ignorance about medical cannabis from the public and the medical community contributes to stigma, which in turn perpetuates misconceptions. The absence of school policies leads to pragmatic challenges within the avenues of cannabis administration and storage in schools; meanwhile the inability to obtain a consistent product from a reputable supplier or the absence of a DIN (pragmatic challenges) make it harder to implement policy.

The lack of data on Canadian children taking cannabis for medical purposes and in schools make it impossible to determine how many children are affected by these challenges. Our study was inductive in nature since no other literature exists on this topic. A qualitative study of pediatric neurologists (in which 58% of the cohort had authorized medical cannabis) identified some similarities, including lack of knowledge, issues with cost, importance of communication, and the need to treat cannabis like other medications [13]. Our work provides a unique contribution by sharing the perspectives of clinicians highly experienced in cannabis-based medicine.

Several limitations of this study should be considered. Recruitment for this study was performed primarily by advertising through professional networks such as the C4T or CCIC that would reach clinicians who dealt with cannabis as a significant part of their practice, but other health care providers were likely missed. Despite recruitment from seven provinces, clinicians from all jurisdictions in Canada would be more desirable; since the support for cannabis and the legislation and policies surrounding its use vary geographically it is difficult to know if this sample is representative of physicians who authorize medical cannabis. Furthermore, we acknowledge that clinician perspectives are only one avenue for exploration. In progress is a follow up study describing the experiences of caregivers of children who require cannabis in schools, while teacher's perspectives should be the focus of future work.

5.6 Conclusion

The culture around cannabis-based medicine for children in Canada is improving, but significant challenges about medical cannabis still need to be tackled. Effective education, communication, family supports and policy refinements that allow cannabis to be treated like other medications are needed. These findings will help to guide future priorities within the C4T Medical Cannabis in Schools working group.

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*More details on study methodology can be found in Appendix A

Table 5.3 Categories and subcategories with additional illustrative quotes

Category	Sub-category	Perceptions about medical cannabis in schools	Perceptions about medical cannabis in general
Variability		Participant 10: *"There's so many cases and variability. I think the bottom line is that we can still don't see standardization from one board to another."* Participant 7: *"Some schools have no concerns or issues, or they just ask some simple questions for us to fill out. And then in other cases, obviously there can be a lot of barriers or a lot of communication that's required. Or sometimes even discrimination around the medicine that they're using."* Participant 4: *"I would say because it's kind of really school dependent, like everybody kind of has different rules and I don't really see anything uniform."* Participant 3: *"With the school, using it in the school has been kind of a mixed experience. I would say that the little kids seem to have less trouble than the older kids in terms of getting it because I guess maybe people are more used to giving older kids medications or they have more problems, I don't know."*	Participant 2: *"I would say most of my patients have a positive experience. If I was to divide it up, two thirds would be positive, a third would be neutral, and a third it doesn't – they choose to discontinue."* Participant 5*: "I'm assuming all provinces probably have different – just like nursing and hospital – policies. I've written a couple hospital policies and again, that changes depending on the province you're in."*
Challenges	**Lack of Knowledge**	Participant 4: *"I find they [the parents] do a lot of the educating because there isn't that formal training that we're talking about for teachers and administrators."* Participant 6: *"Historically there's always this high anxiety about administrating cannabis, and the irony of it is that the same people who are worried about it are administering drugs that can actually cause very, very severe side effects that are far worse than cannabis. So, there's just a lack of education, I think, overall on the risks and benefits of it."* Participant 1: *"I can only presume the schools know nothing. Like literally nothing. And then that is reinforced by some of the stuff that comes back to me about this on the negative side whereas again."* Participant 2: *"There's definitely misconceptions that their child will be high."*	Participant 3: *"Unfortunately there's this Google world out there and a lot of misinformation on the web. So most parents are forced to gather the information through the internet, or chatting about experiences with their peer groups."* Participant 1: *"I run an education session every week with parents and 90-99% of them know nothing about what I teach them."* Participant 4: *"Even physicians still, some don't have any clue that this is going on with these patients."* Participant 6: *"And it's no fault of their own GP or specialist, there isn't the education for a lot of physicians out there."* Participant 1: *"I speak to physicians who know nothing about this stuff. Like literally zero. And it's a product of the medical education system, too in this point in time."*
	Stigma	Participant 12*: "There are parents that do not mention that their child is on CBD to friends and family members, and they don't say the child is in CBD in school."* Participant 4: *"It's difficult in that people are just kind of uncomfortable with it even being at school even though usually we're talking about CBD."* Participant 3: "*They [schools] don't like the term cannabis at all. Even though it is CBD which is non-psychoactive."*	Participant 11: *"I think different families have different opinions about cannabis, for sure. Opinions are really polarized."* Participant 10: *"I know there's some pediatric neurology divisions where they still say no, as a group we're not authorizing it. Patients have to get it somewhere else."* Participant 6*: "Gabapentin's used 99.4% off-label… It's in the top ten prescribed medications in the world. But do we say there's not enough evidence to use it? No. So let's put cannabis at the same level in the real-world of how we actually practice medicine, and not be so narrow minded to say it doesn't exist as the possible treatment because we don't have those levels of evidence."*
	Lack of Policy	Participant 12: *"I don't think there is a policy in the province, and what I've seen is in some schools, the teacher or the principal will be open enough to allow giving it, or not. It's purely institution-based and person-based even."* Participant 3: *"The school board is responsive to both the catholic school or public school, and they both have community boards of trustees. And they're kind of risk aversive around that area. Beause if they have a policy, then it applies…and they're pre-2000 policies that just have to do with recreation use, not therapeutic use"*.	Participant 3: *"When Mr. Harper put the policy in place, they kind of just dumped it on the market – it's like, you're three quarters of the way there and you just stop. Beause to get all the way there, they should have said 'okay here is our plan, we're gonna approve it and here is how you get a product monograph and everything else.'…So there's 360,000 prescription drugs in Canada, and cannabis. Health Canada has approved them all, but there's this one. So they're sitting out there totally different than all the other drugs."*

		Participant 4: *"There is no policy. Depending on who's leading the school they might have their own personal view which is the defacto policy."*	Participant 11: *"It's really the wild west out there. For me to try and help people navigate that and try and understand all the different products out there and which ones are most reliable or most reputable, there really hasn't been a lot of guidance around that."*
	Pragmatic challenges	Participant 1: *"Around administering the medication, who's going to take that responsibility from school and then what is going to be the result of the administration of medication during school hours?... There's hesitancy around administration or permitting administration of cannabis in schools."* Participant 7: *"There's some facilities that (this is more in older students) they don't like a liquid. They prefer capsules that they can give and just count the capsules rather than trying to measure a liquid. I've encountered that on a number of occasions. And sometimes that works, but sometimes that doesn't because people can have various medical reasons or disabilities that don't allow them to use capsules, or it's not the right approach. Like liquids would be better for more fine tuning the dose."* Participant 3: *"I would say the biggest issue is storage, secure storage. Because since we no longer have things like school nurses… in most schools it's just a first aid kit sitting on a counter… And the one situation I remember they actually used the principal's office because there was no other secure place that they could store it. But there was a locked cabinet in there."* Participant 7: *"Well the number one issue is paperwork. It creates a lot of paperwork for me which obviously decreases the amount of facetime I can have with patients and not a big fan of paperwork. So, there's no standardized options, there's no one size fits all that I could streamline or automate which could be helpful. But the number one pain point for me is just the paperwork."*	Participant 3: *"The other issue with administering it with the younger kids, is that medical cannabis is just an unpleasant product. It tastes bad, it smells awful, CBD oil is horrible… it is not a child friendly pharmaceutical to frame it diplomatically."* Participant 12: *"Cost is quite important. Many of these children are on several medications already. Some are taking a ketogenic diet… it's not cheap. And then, most of the time one of the parents need to stay with the child 24/7 because for safety. They are not really having two parents working in the household. It's only one. It's way beyond just economical. It's a whole social situation. And these families are very fragile, having a child with a chronic disease. Many parents get divorced because they cannot cope very well with the situation."* Participant 11: *"Cost for sure is a factor for my families. Especially here, lots of low socioeconomic status families not covered by drug plans. People are paying out of pocket for it. We also serve a lot of kids in foster care. And so far, there's been zero appetite for those kids to get approval to use cannabis products at all, so that's a group that's been excluded and in some ways they're one of the higher needs groups who might benefit the most."* Participant 10: *"It is time consuming. There's always forms that you have to fill out. The biggest challenge is trying to figure out, based on the dosage of CBD that I want to authorize, how many grams of dried cannabis per day matters that can be a bit of an issue."* Participant 9: *"It's so expensive for parents. It's prohibitive for most families. Many parents will confess to me that they have actually gone into a legal dispensary and basically bought for themselves cause they're over 19, but they've given it to their child."* Participant 11 *"I'm sort of sending people and saying 'Well, you can get it online, you can get it at the government store. And when you go online, maybe the products that will be available this week are different than last week, therefore be prepared for there to be shortages. You may have to send me a picture of what you buy so we can make sure we know what you're on and what the dose is so we can help you with the dosing'. So yeah, for sure it's a lot more work. Because people have such a variety of choices and not everything that I recommend may be available, we have to be flexible and nimble with the dosing."* Participant 3: *"And the problem of the clinician, is you have to pick out which is a reliable supplier because no disrespect, but this is not like prescribing something that's on the CPS…So, you have to find a manufacturer, a supplier you're confident with."* Participant 5: *"A lot of these kids- especially with autism- they have difficulty with pills or capsules. They also have texture, teeth sensitivities. It can be very challenging, even for the parents to be able to administer that."* Participant 3: *"Medical cannabis is just an unpleasant product. It tastes bad, it smells awful, it's just not – CBD oil is horrible. I mean it's good if you can get it really concentrated form cause then you can just get it over with, with a couple of drops, but it is not a child friendly pharmaceutical to frame it diplomatically."*

Improve-ment over time		Participant 3: *"I think people are more open. I think schools are more open to medical cannabis than they were before."* Participant 7: *"I would say that the tide turned about five years ago. Maybe less than that. About four years ago. I think if up to five years ago if it was known that a child was on cannabis, that probably would've raised more alarm bells then, and more resistance. And I think that at that time, parents probably weren't as open about what their kids were doing at school…But that stigma has thankfully been reduced dramatically."* Participant 10: *"I think they [teachers] still need education, but it's getting better. It is definitely improving."*	Participant 12: *"A few years back, we had a policy that CBD was not prescribed by our hospital... But that had a gap because the physician who was prescribing the medication may have had no idea about epilepsy, and we that had the idea, in theory to handle, were to able to. But a couple years ago, our hospital opened up a little more in the policies with all the clinical trials that were published. We now have a protocol and I'm able to authorize it."* Participant 11: *"I think people are increasingly open to the possibility of using it as a therapeutic agent. For sure I think five years ago there would have been very few takers, and now it would come up regularly in my clinic as a topic of discussion. I think people are increasingly being open to it especially when they hear about other families or other family members who have used a cannabis product and have used it successfully and it's been helpful to them, so I do think people 111ecomeoming more open minded to that possibility as time goes on."*
Potential solutions	**Treat it like other medication**	Participant 2: *"The school requires the product to be from a licensed producer. They require a prescription which we negotiated as being a prescription alongside it... And then they treat it like any other medication. So, amoxicillin, they have a special place in the school for it. It's locked up, it's used exactly according to the directions, and that's exactly what they do with the cannabis products."* Participant 7: *"Like any other medication if it's required during school hours, we have to find a way to get that into the child…I would always educate them on that human right…and the school should do their best to accommodate that need, and we can also do our best to accommodate their limitation."*	Participant 10: *"This is like another medication… It should be formalized, this is another medication."* Participant 1: *"That [a DIN] would make my life incomparably easier because then you could prescribe prescriptions like a normal person."* Participant 10*: "I think the medical cannabis indust–y - if they want to be considered like a drug company, like a pharmacy - they need to set themselves the same standards."* Participant 13: *"This is just another drug."*
	Education	Participant 2: *They [the schools] weren't informed at all, but they were very open to education. And a lot of them are blown away that I would just come and on my own time, come and educate them. And that has gone so far with making people comfortable, making it so that they'll actually be willing to work together."* Participant 4: *"Communicate and educate, I would say. Because again, I find they do a lot of the educating because there isn't that formal training that we're talking about for teachers and administrators"*.	
	Commun-ication	Participant 3: *"I think the big thing is communicating – clear communication, documentation. Communicating with the schools, document what's going on, show the documentation. The schools have to understand what your plan is, you have to understand what the schools concerns are, you have to document how you're gonna address those things, and then you go forward keeping communication open. So if the school has an issue, they'll tell the parent, they should be able to communicate with you and say 'listen, this isn't working for these reasons, what can we do to get the wheels back on the track?'"* Participant 9: *"I think the physician, is part of the navigation process and we'll tell the parents to speak to the teachers and the principal. And ask about the policy in the school and what documentation is required."* Participant 4: *"Don't get frustrated if you might have to have multiple meetings. Be patient. Explain things clearly."* Participant 1: *"Probably in a stepwise manner – have the parent discuss specifically with the teacher to inform the teacher of reasons why cannabis is being used and what it's about and – if the outcome or the objective is achieved, then that's fine. If not, next level would be the administrator, the principal. And if that outcome is achieved, then the*	

		principal educates the teacher and therefore you have a nice network. If that is not, then the patient or parent should go to the doctor and the doctor should then communicate with the administration at school. I would say that would be a three-step process that would probably make the most sense." Participant 7: "*It's just really important to keep really good documentation to make sure there's no misunderstanding, confusion, mis-dosing, or medical errors."*	
	Support for Families	Participant 3: *"And I guess they [parents] need some level of diplomacy working with the school staff. So I think they have to be patient, they have to be persistent, and they have to have access to resources and also the ability to negotiate around solutions that will work for the patient... They need the ability to deal with bureaucracy."* Participant 7: *"I'm a big fan of patient support groups. The perspective of another parent having a child using medical cannabis and then trying to figure out how to navigate the school system is really, really helpful."* Participant 2: *"I tell parents to just not get into arguments about it, to just put them on the phone with me because I find the more people get worked up about it, the less likely we're gonna get anything done. If I can just get in there right away and have direct conversations, everyone chills out and everything goes better."* Participant 8: *"I get barrages of texts all the time. But some of them are really legitimate and a crisis and I've learned a lot from that. But I think just to prescribe it and give someone a prescription and tell them how much to take with no follow up, I just think that's really bad medicine."*	Participant 3: *"I think they need a lot of support. And one of the reasons that I stay in very close contact with my patients and their families."* Participant 7: *"It's through peer sharing. It's talking to other parents in the same situation that have had a good experience. That's probably the best knowledge they can get."* Participant 5: *"You need to be referred to a cannabis specific clinic… I appreciate and I'm supportive of family doctors learning how to do this and wanting to support their patient and have that longitudinal relationship, but if a family doctor's only got one or two people doing this, it's not really fair to the patient – the physician doesn't know enough of the day-to-day shortcomings or what can happen to be able to support that patient.… So again, it's having an experienced clinician that's working with the family and being supported by that clinic."* Participant 6: "*Just trying to find a physician that has experience and is comfortable with the process [is a challenge]. There are some other resources out there that are…more possibly for profit as business. And you can go to these places and get an authorization in 30 minutes or less, any quicker than a pizza. But is there necessarily the information? Is there necessarily the follow-up?"*

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CHAPTER 6. MEDICAL CANNABIS IN SCHOOLS: THE EXPERIENCES OF CAREGIVERS

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All authors contributed to the study conception and design. The data collection was performed by ZZ. The analysis was performed by HM, SM and PMK. HM drafted the manuscript. ZZ, SM, TK, LEK, TL, JA, RH and JA critically revised the manuscript and have approved the final version to be published. HM was the corresponding author.

6.1 Abstract

Background: Implementing medical cannabis into a child's daily routine can be challenging and there is a lack of guidance for its therapeutic use in schools in Canada. Our objective was to learn about the experiences of caregivers of school-aged children who require medical cannabis.

Methods: Qualitative description was used and caregivers were interviewed about medical cannabis in schools and in general. The transcripts were entered into Dedoose software for qualitative analysis and content analysis was performed. Sentences and statements were ascribed line by line into meaning units and labelled with codes, and organized according to categories and subcategories.

Results: Twelve caregivers of school-aged children who take medical cannabis participated. The most common reasons for treatment were drug resistant epilepsy (DRE), autism, or other developmental disorders. Approximately half of the participant's children (n=6) took medical cannabis during the school day and most (5/6) perceived their experiences to be positive or neutral but reported a lack of knowledge about medical cannabis. While data saturation was not reached regarding medical cannabis in schools, rich dialogues were garnered about medical cannabis in general and three categories were identified: challenges (subcategories stigma, finding an authorizer, cost, dosing, and supply); parents as advocates (subcategories required knowledge, attitudes, skills, and

sources of information); and caregiver's relief for positive outcomes.

Conclusion: Caregivers demonstrate remarkable tenacity despite the many challenges associated with medical cannabis use. Education and practice change are needed to ensure that children using medical cannabis can benefit from or continue to experience its positive outcomes within the school environment and beyond.

6.2 Introduction

The awareness of cannabis use for medical purposes has increased drastically in recent years [1]. Research advancements suggest that medical cannabis has a legitimate therapeutic role in some children or youth, particularly to decrease the frequency of seizures in certain types of DRE, alleviate chemotherapy-induced nausea and vomiting or chronic pain, or ameliorate behavioural symptoms in conditions such as autism spectrum disorder [2-4]. Medical cannabis is typically reserved for patients who experience severe symptoms that are resistant to traditional treatments, and is often a last resort treatment option for families [5,6]. It should be noted that there is an urgent need for more prospective studies to examine safety and efficacy of medical cannabis of children.

Caregivers and clinicians who provide care for these children attest to the need to treat medical cannabis like any other medication [5,7]. However, unlike other prescription medications in Canada, medical cannabis does not follow the regular drug review process or have a Drug Identification Number (DIN) [8]. As such, medical cannabis is not placed on provincial or territorial drug formularies and insurance health plans do not consistently cover medical cannabis, additionally caregivers report barriers with access to supply [9]. With a complicated history due to prohibition and a policy emphasis on recreational use, misconceptions about medical cannabis remain prevalent and a there is a lack of knowledge amongst the general population and health care providers [7,9-11]. As such, implementing medical cannabis into a child's daily routine can be challenging, especially for those who require a dosage to be administered outside of the home [7]. In a recent scoping review, we identified few publications and policies on medical cannabis use in Canadian schools [12]. A qualitative study of clinicians who authorize medical cannabis to children concluded that significant enhancements are needed to improve support for caregivers and children who require it in schools and in general [7]. The present study aimed to learn about the experiences of caregivers of school-aged children who require medical cannabis.

6.3 Methods

Methodology and recruitment

The study followed best practices for undertaking and reporting qualitative research [13,14]. We used qualitative description, a methodology which aims to explore a phenomenon of interest using participants in a particular situation and describes a rich description of the experience in an easily understood language [15,16]. Advertisements and invitation letters were shared through various Canadian websites and social medical channels to reach the target audience of caregivers for school-aged children and youth that require medical cannabis. Potential participants were encouraged to share recruitment materials. A Survey Monkey link remained open from August 2021 to February 2022 for interested participants to provide their contact information to the study team.

Interviews

A semi-structured interview guide (Table 6.1) was developed by The Canadian Collaborative for Childhood Cannabinoid Therapeutics (C4T) "Medical Cannabis in Schools" working group members, which consists of parents of children who take medical cannabis, physicians who authorize medical cannabis for children, community health nurses, and a pharmacist (n=10) [17,18]. Z.Z., a researcher with previous experience in qualitative research, conducted the interviews, which were continued until all open-ended questions were answered and the participant had nothing else to add. The interview guide was structured around questions about medical cannabis in schools, but allowed for flexibility to explore topical trajectories about medical cannabis in general as they emerged within the dialogue. A $25 gift card was provided to the participants in appreciation of their time.

Data analysis

Eleven interviews (transcribed verbatim) and the notes of one interview (which was not recorded by request of the participant) were analyzed by three researchers experienced in qualitative analysis (H.M., S.M., P.M.K.). Qualitative content analysis [19] was used to analyze the data using Dedoose [20] to organize the data. All transcripts were reviewed initially by the researchers. Sentences and statements were ascribed line by line into meaning units and labelled with codes [19]. The codes were subsequently organized according to categories and sub-categories. The researchers met multiple times throughout to iteratively review for category relabeling and refinement until the results were collated into a final manuscript. Participants were sent a copy of the report with an opportunity to provide feedback prior to publication.

Ethics approval

The Behavioural Ethics Board at the University of Saskatchewan (Beh# 2804) approved the study and consent was obtained by participants.

Table 6.1 Semi-structured interview guide for caregivers

Introductory Questions	Tell me about your relationship to the child(ren)/youth that is (are) using medical cannabis in schools and in general?
	Describe the situation for which the child/youth is using medical cannabis in schools and in general?
Exploratory Questions	Describe your child's experience with using medical cannabis in schools?
	What (if any) are the requirements for your child to use their medical cannabis at school?
	What was easy or difficult for your child about using medical cannabis in schools and/or in general?
	What was easy or difficult for you as a parent using medical cannabis in schools and/or in general?
	Please describe where you receive your information about medical cannabis from.
	How well-informed do (or did) you feel the school was about medical cannabis for children/youth?
	What information do you think is important to know for teachers or school administrators to know about medical cannabis for children/youth?
	What skills do you feel a parent/caregiver requires to navigate medical cannabis in schools, and/or in general?
	Are there any supports that you benefited from? Are there any supports that weren't available that you could have benefited from? If so, please describe.
	If you had to tell another parent or clinician how to navigate medical cannabis in schools (or in general), what would be the key things important for them to know?
Exit Question	What else do you want me to know about your experience with medical cannabis for children/youth in general?

6.4 Results

The research team followed up with 30 individuals who who provided their contact information to learn more about the study and 12 were reached and agreed to be interviewed. The interviews lasted between 18 and 40 minutes, and 10 were conducted by phone and two by video conference. Participants included parents of children who were taking cannabis oil or pills authorized by a health care provider, [either cannabidiol (CBD) alone or CBD and tetrahydrocannabinol (THC)] primarily for DRE and/or Autism and developmental disorders. (Table 6.2)

Table 6.2 Participant Characteristics (self-reported)

Characteristic	Number (%)
Age	
20-29	1 (8.3%)
30-39	4 (33.3%)
40-49	5 (41.7%)
50-59	2 (16.7%)
Sex and Gender	
Female	11(91.7%)
Male	1 (8.3%)
Province of residence	
British Columbia	4 (33.3%)
Alberta	1 (8.3%)
Ontario	6 (50.0%)
Nova Scotia	1 (8.3%)
Occupation/profession*	
Healthcare professional and paraprofessional healthcare support worker	6 (50.0%)
Teacher or academia	2 (16.7%)
Home business or other	3 (25.0%)
Stay at home parent*	3 (25.0%)
Race	
Caucasian	11(84.6%)
Visible minority	1 (8.3%)
Child's sex	
Female	5 (41.7%)
Male	7 (58.3%)
Child age (years)	
4-5	5 (41.7%)
6-12	2 (16.7%)
13-18	5 (41.7%)
Indications*	
Treatment resistant seizure disorders	9 (75.0%)
Autism or other developmental delay	7 (58.3%)

Chronic pain, palliative care, cancer	1 (8.3%)
Child takes cannabis during the school day	
Yes	6 (50.0%)
No	6 (50.0%)

*Percentage will not add up to 100 since some participants stated more than one answer

Medical cannabis for children at schools

Approximately half of the parents who participated had children (n=6) who took medical cannabis during the school day. Of those who did not, most (n=4) indicated that the schools were aware their child was on medical cannabis and didn't perceive any barriers should school-dosing be necessary. Participant 1, however, anticipated resistance from the school, while participant 6 said "*There's a zero-tolerance marijuana policy at his school. I've just been kind of too scared to bring it up with them because I don't want it to be an issue. We have already gone through so many issues with school already.*"

Five families that required medical cannabis administration at school perceived their experiences to be positive or neutral and did not report encountering barriers. The requirements for medical cannabis (e.g., paperwork, packaging, labelling) and person responsible for administering the dosage (teacher, educational assistant, or health care provider) varied with the institution. One school, however, administered all medications except medical cannabis, which necessitated the parent to drive to the school at lunch hour to administer the mid-day dosage to their child. Caregivers commented on some of the additional fears surrounding medical cannabis. Participant 11: *"There seems to be a real push to keep the cannabis under lock and key. Some kids can just keep their medications in their backpack or perhaps at the teacher's desk, or in the office, but the cannabis needs to be put away, away, away. I think that's just silly at this point, especially an oil… I think a lot of the fear is making it harder for families just to go out on a day trip or to school."*

In general, participants did not perceive teachers and administrators to be well-informed about medical cannabis as they learned about it only on a case-by-case basis. According to participant 3, *"It was pretty much completely on me to inform them about it and* *educate them about it, which is fine. I didn't expect them to be knowledgeable about it. But yeah, I would say their prior knowledge to it was close to zero."* Participants were queried about what they believed schools should know, and whether they had advice for others in their situation. (Table 6.3). According to participant 1 "*cannabis should be treated the same way as any other medication*", and this sentiment was echoed by the others.

Table 6.3 Information about medical cannabis that participants deemed important for schools and other caregivers to know

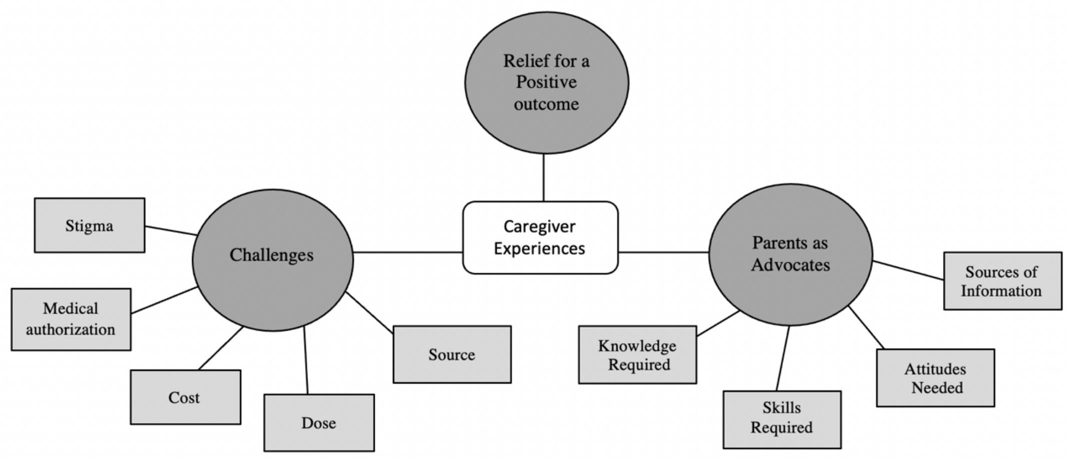
Important principles for medical cannabis in schools	- Schools should be supportive and non-judgmental - Stigma around medical cannabis should be eliminated - Schools should not be able to turn medical cannabis away if it is under the supervision of a physician
Important information for teachers and school administrators	- Medical cannabis is a medication; and it should be treated the same way as any other medication - What medical cannabis is used for medically - How medical cannabis works - The benefits and safety profile of medical cannabis - Up to date research on medical cannabis - The abuse potential of medical cannabis is very low
Tips for other caregivers to navigate medical cannabis at schools *(in the participant's own words)*	- *"Make sure that there's meetings and discussion on why it's needed and understanding the importance of it ahead of time. Like well before school starts so everybody's on the same page."* - *"I would say the key thing is to research and get the statistics, and don't go in combatively."* - *"I think that you have to have a lot of confidence in what you're doing. I think that you almost need to go in with a sheet with key talking points, that's what I did. And a lot of medical information because everybody loves research. And I think for me it was just the relationship I had with the school, but also the fact that I went in very scientifically, or as scientifically as I could in terms of promoting 'this is why we need to do this'."* - "*You definitely need to be able to communicate and advocate for your child."* - *"I rarely call it medical marijuana; I call it her prescription. And I think just that little mindset, that little change in*

	terminology, that little nudge in that direction can really, really help.” - *“Communication…so that you know if he has his dose, if he missed his dose, because if he needs another dose later in the day. Maybe using a communication book to pass back and forth each day [between schools and parents]”*

Medical cannabis for children in general

Three main topics emerged consistently throughout the dialogue about medical cannabis in general: 1) Challenges; 2) Parents as advocates; and 3) Caregiver relief for positive outcomes. Additional supporting quotes are found in Tables 6.4 and 6.5. Figure 6.1 provides an overview of the categories and subcategories.

Figure 6.1 Overview of categories and subcategories pertaining to caregiver experiences with medical cannabis



1) Challenges

Caregivers encountered numerous challenges related to medical cannabis. The majority (n=8) recounted stigma with physicians, school administrators and staff, and/or family; but many acknowledged improvements as medical cannabis use has become more common. Some participants described how stigma decreased once the benefits were realized. For example, participant 2 said, *“My family physician went from absolutely I’m* *not touching that to wow, he's doing incredibly. She did a 180 based on my son's experience."*

Caregivers were often met with resistance when discussing medical cannabis with their physician. Finding a suitable authorizer was perceived to be a major barrier (n=7) and they had to seek out multiple healthcare providers to achieve a positive outcome. Participant 7 shared, *"We had been asking to try CBD oil with our neurologist for a year and it was a strict no. They felt like there wasn't enough research for its use and that we should be using these other medications that have pretty terrible side effects."*

Parents described other challenges, such as finding a place to obtain the medical cannabis and determining the appropriate dose for their child's needs (n=5). Some highlighted their use of trial and error to find the correct dose. Participant 6, *"The doctor only did the set up. Everything else, like the dosage and everything, that's for me to figure out by myself. I find it really hard to find information on dosage because if you ask on the Facebook group, everyone will always tell you it's different for everyone. You can't just have a set dose."*

The high cost associated with acquiring medical cannabis was voiced by nearly all participants (n=10). For some this was *"about a mortgage payment per month"*. In other instances, medical cannabis suppliers subsidized the cost. As stated by Participant 10, *"we did have to pay like $1200, $1000 for the first couple prescriptions. But then we found [supplier] where they give the youth program… And now it's $540."* Participants expressed the need for insurance coverage to include medical cannabis as cost is barrier for many families.

Table 6.4 Challenges: Additional supporting quotes

Sub-category	Quote
Stigma	Participant 2: *"Slowly things are becoming more accessible. As you know, medical cannabis is not in the mainstream and physicians are well outside of where they should be because they don't have the training. They're obviously terrified to prescribe it. But some will refer to a prescribing physician. So if referrals are happening, that's a positive change…But since it was legislated, there's been a bit less stigma attached to it. But we have a long way to go."* Participant 3: *"I've talked to lots of other parents who've faced a lot of stigma and negative whatever you want to call it, emotional attachment. We have not really experienced that. And again, I attribute that to the fact that when we started cannabis oil for [child name], we were very, very open and transparent with everyone, including the school board, about why this was being done and the purpose."* Participant 4: *"We were trying it for a while… And when she had her first seizure, we took her to the hospital and again, this was about four or five years ago, and I thought they were gonna call Social Services on me, to be honest with you. When I told them this is what she takes for mediation and stuff. It was interesting because four or five years ago when we first talked about it with a physician it was like 'Are you crazy!? What are you doing?' And now it's way more commonplace."* Participant 5: *"My immediate family, extended family just thought I was bonkers. But at the end of the day, you're the parent, you make the decision. And in my opinion, the benefits outweigh the risks…I don't really understand the stigma, to be honest, but it's definitely there. It's definitely there, for sure."* Participant 6: *"Yes, it's privacy and stigma. Honestly, when he was little, we used to be very open with the school about his medicine and sometimes we would say maybe we're thinking about not giving him medicine anymore and then the people at the school would be all freaked out and scared. Then they would try and give us their opinion, and they're not doctors, I can't really take their opinion into account. I try and keep that information private."* Participant 7: *"But even with family, I think we had – my mother-in-law, father-in-law, they're in their 70's, so they were a little bit nervous about her starting it. But then once they saw how good seizure free was, they were very accepting about it so far. It seems like most people support it, and we get a lot of people messaging us with articles, asking us if [child name]'s on CBD because they see articles about it helping epilepsy. It seems much better now than it would have been ten years ago, I think."* Participant 9: *"But I don't think we ever encountered any stigma because we had a valid reason for using it and most people have been very open, even her neurologist has never given us a hard time even though the neurologist will not prescribe any cannabis.* Participant 10: *"…I mean I feel like a lot of people are coming to be more accepting of it, but there are still a lot of people that don't want to open their eyes until it's actually in their hands, you know what I mean?"* Participant 11: *"We started our child before he turned one on cannabis. At that time there was a lot of stigma between using cannabis that what kind of family would we be to have our one year old using it? And no one was even calling it cannabis, everyone was calling it marijuana at that time. There was a lot of stigma around it… so it's much better right now."*
Medical Authoriz-ation	Participant 7: "*We had at least three follow-up appointments where we asked about CBD each time and every single time, we were basically given the answer there's not enough research to support it, there's too much research to support these other meds which [child name] was already on and weren't working. They just wanted to keep increasing these other meds."* Participant 2: *"The easiest part of our journey was to get it administered at school…Access to practitioner that would take on a pediatric case, that was the huge stumbling block and barrier…The fight was to find a supervising doctor at the very early stages…That's the biggest barrier for families."* Participant 9: *"I do know that there has been a lot of pushbacks from the pediatric association and the X medical association about not prescribing it for children because of a lack of data."* Participant 11: *"When we started looking for someone to give us our authorization, we had to talk to quite a few people who were either against it or their authorizing board would not allow them to. So, our neurology team at the [hospital] was, at that point, not allowed to write prescriptions or the authorizations for cannabis until very recently. We did find a family doctor who recognized that this would benefit [child name] and when we started, under the program that was then available in Canada to use medical marijuana."* Participant 3: *"In terms of outside researchers and clinicians, I think the biggest hurdle is just acceptance and respect of it as a medicine just like any other medicine."* Participant 5: *"But our primary pediatrician didn't wanna put him on it. We actually had to go to [name] clinic which is the clinic where they prescribe cannabis to children, adults as well."*

	Participant 1: *"We had a lot of challenges with access just in terms of getting a referral to somebody who would authorize."*
Dosing	Participant 4: *"It's the mad professor to start and that's the whole thing about medical cannabis is you have to be able to put the time in. You have to have incredible records, like finite recordkeeping. Because you need to know, or at least what our experience was, is we need to monitor when she's coming a little bit down off that."* Participant 5: "*We started him of course at a lower dose, it was a trial-and-error thing, I found. We had to play with the dose a lot before we could figure out what really worked."* Participant 2: *"…but the poly pharmacy with the CBD is new territory, tricky, tricky for navigation.* Participant 1: "*Just challenges with consistent dosing. Not able to do, let's say six hours apart. And then there were some days where he was going to after school care, so I just wanted to keep things consistent so that it wasn't being given at different times different days."*
Source	Participant 6: *"I think accessing it, is a little bit tough, I find. Because when I found the – for example, we buy a certain brand, it's called the [brand name] and it has the proper terpenes or whatever, and we're hoping will be beneficial for him. Sometimes it's out of stock at [supplier]. And I can't just go to the dispensary and buy it, as far as I know, because I heard it's illegal to do that. You have to order it from a proper supplier to have the sticker on it with his prescription or whatever."* Participant 1: *"We use the two different dispensers because we also found since it's become legal for recreational use, the supply has become iffy. Sometimes they have what we need, sometimes they don't. We've gone between two different ones to be able to consistently get him the oil at the right level that we need."* *Participant 2: "We're on our fifth licensed producer and now it's right. That's the journey, right? And now it's right, and so we're here with a product that hopefully will be the last producer that we need to find."*
Cost	Participant 1: *"And in terms of cost, I think there's a very unethical healthcare inequity because it's an uncovered benefit for nearly everybody and the out-of-pocket costs are high, so it's only accessible to those who aren't sort of low on the rank of the social determinants of health."* Participant 7: *"The youth program at [supplier] was a percentage off. I would order $800 of CBD and pay ten bucks. It was insane. Maybe that's why they had to cancel it because it was too intense for them. But the one that I'm ordering from now, we get $200 off every order."* Participant 3: *"Yeah, so the cost is a big barrier obviously. I've been lucky enough to be able to pay for it because it's not covered by any insurance. The cost right now for my daughter, [child name] is approximately $450 a month…But yeah, it's definitely cost is prohibitive in many ways."* Participant 5: *"And it's not even like you buy aspirin on the counter and it's like eight bucks. We're talking about 50, 60 bucks a bottle. That's really so much money…Financially, my husband and I can manage it, but he's only five. It's already quite expensive. I'm imagining the dose is probably going to have to go up as he gets older. What's that gonna look like? I don't know.*" Participant 2: *"So our cost is about – the shipping's 20 dollars. It's about $100 a month. And I know there's expenses that are way higher than that for some families…."* Participant 6: *"That took several months of me emailing and texting the social worker. And the social worker's supervisor, pushing for them to give him a chance. Because I knew I wouldn't be able to afford it by myself."* Participant 9: *"The thing is that some of the anti-epileptics that my daughter takes, it's $16 a pill. And so that is covered, yet a $90 bottle of cannabis that lasts us ten days isn't. And so, who's to say for another child that doesn't have the means, the parents have the means to provide that.*" Participant 10: *"If we have run out of her prescription, we are allowed to go to the liquor store and pick up the closest ratio. But it is way more expensive. So right now, her bottles like 46.99 through [supplier] and then if I went to the liquor store, it's almost $70 for a bottle.* Participant 11: *"Definitely it's his most expensive drug and the drug plans aren't covering it. So being that he's taken it for many years, like any medications, he's needed more and more to help control his seizures. And with it becoming legal and the government taxing it, it's actually become more expensive in the past couple years than ever before. So yeah, I think the drug plans need to get on that it's being used as a medication and that if it's being used medicinally with a prescription, I don't think the government should be using it as if it's recreational. It's definitely 100% the cost is a barrier."* Participant 4: *"And I mean, we'll do whatever we can do and we're lucky, but 400 bucks for some people is their groceries…It's too bad it wasn't covered."*

2) Parents as advocates

Parents described having to continuously advocate to access medical cannabis. To overcome obstacles, they acknowledged the need for themselves to be well informed and possess key skills to ensure their child's sustained medical cannabis use. According to participant 2, *"Parents must take on the task of being well-educated and well-read and then advocating on their child's behalf in a big way."* Extensive knowledge about cannabis and physiology was perceived to be important, with an ongoing commitment to keep informed about research and to act as an educator (when needed) to their healthcare providers and others within their circle. Effective communication was perceived to be essential, including the ability to tailor conversations and speak carefully and articulately to change mindsets. The need for a *"thick skin"* to manage criticism and stigma; tenacity and confidence to "*speak up"* in advocacy; and therapeutic management were skills and attitudes required to "*sustain the journey*".

Parents described accessing information and support from several sources. These included online websites, social media, support groups, dispensaries, word of mouth, TedTalks, television and movies, supervising physicians, interprofessional teams, perceived experts, and other parents who have been successful in securing medical cannabis for positive outcomes. They were eager to gain information from the lived experiences of others and to support other parents encountering challenges. Clear support from an interprofessional team and working collaboratively was perceived to contribute to success.

Table 6.5 Parents as advocates: Additional supporting quotes

Sub-category	Quote
Know-ledge required	Participant 2: "*To be well read and to get current research that's peer reviewed...it is an art and a science. It's not a magic bullet."* Participant 3: *"So, number one thing is be clear about your intentions for medical cannabis and speak as clinically as possible so the doctor can relate to the information that you're trying to convey to them....Unfortunately, in order to do it successfully currently, there's a lot of knowledge required by parents that most people don't have, like education about neurology or arthritis, or the endocannabinoid system in general, or how to access it, what is the legal requirements, where to get it, who can prescribe it. Unfortunately, currently if you're a caregiver trying to help someone that might benefit from medical cannabis, you need to know a lot more than you should. And hopefully – you know, it's changing as we go, and hopefully it keeps changing because parents shouldn't – well anyone who isn't a neurologist or a doctor of any specialty, whether that be research, clinical, or whatever, shouldn't have to know biological fundamentals in order to get the medical treatment they deserve."*

	Participant 1: *"There's no roadmap or algorithm to follow to navigate this."* Participant 5: *"You have to know what it is you're using, why you're giving it to your child."* Participant 2*: "They have to read, read, go to these workshops, talk, talk, talk to people. Pick up the phone. Read online, get rigorous peer reviewed journals and articles and incredible research has to be done by the parent."*
Skills required	Participant 1: *"...willingness, advocacy skills, and the ability to be empowered to move beyond status quo. Healthcare literacy and multi-system perspectives and historical context…understanding that this is a systemic issue and it's not a personal one. Acceptance, flexibility, assertive communication skills and the ability to connect, collaborate, educate, and a good strategy. Strong support network, personal resiliency and self-efficacy, to value your own autonomy, to have hope, vulnerability, authenticity, humility, courage, intuition, active listening and curiosity, and dedication. [Laughs]. Just a few things."* Participant 3: *"Well, currently I guess the most important skill would be good communication skills so that they can speak to their doctor."* Participant 4: "*I've always used the word advocate, and that's the big thing when you're a special needs parent is you have to be able to advocate for your child. And I've always gone in with a reasonable approach."* Participant 5: *"Skills, I mean you have to have a thick skin, I think. Because there's a lot of criticism* Participant 1: *"Sometimes you just have to embrace your inner troublemaker to get stuff done and evoke change."* Participant 3: "*Number one thing: If you're gonna speak to your doctor about cannabis, whether it's for you or your child or someone else you're caregiving for, my advice is always speak as specifically as possible, talk to your doctor in as clinical terminology as you're capable of because no doctor's every gonna listen to someone who comes in and says this is gonna fix everything and this is some kind of magic! This is not a part of the lexicon of scientists or doctors."* Participant 7: *"You definitely need to be able to communicate and advocate for your child because if there is pushback and somebody's not comfortable administering CBD – it's different if they're not comfortable administering any medications. But if it's like oh, I'll give you these three meds but not CBD, you have to be able to advocate and fight for your rights and communicate and understand. Give people the research. And I think not all parents would be able to do that. We were ready to do it, but fortunately for us we didn't have to."* Participant 5: "*To be proactive, but I think that's basically when you have a kid on the spectrum, you have to be really proactive anyway so it kind of goes with the territory."* Participant 2: *"They need to be advocates, so they need to really fight to get a supervising doctor. That was a huge fight for us because people are resistant in the community – medical community – to even go there, cause their licenses are on the line if they start to dabble in something that they don't have the education for. So the parents need to advocate for their child's needs. And then they need to be incredible researchers."* Participant 10: *"Definitely critical thinking and they need to navigate the system because it's not a cut and dry system."*
Attitudes needed	Participant 1: *"…That it's a pilgrimage that the systems broken, so try not to take it too personally and at the end of the day, it's the welfare of your child or patient and your own integrity that matters most. Your silence serves no one and I just love this quote, stand up for what you believe in even if it means standing along."* Participant 4: *"I think that you have to have a lot of confidence in what you're doing."* Participant 2: "*Because every child's different and every adult's different. It's not a magic bullet, medical cannabis. It's a unique journey of trying products and seeing if they fit for the individual…We're on our fifth licensed producer and now it's right. That's the journey, right? And now it's right, and so we're here with a product that hopefully will be the last producer that we need to find. But it wasn't a small journey, let's put it that way."* Participant 10: *"I think in order to navigate the system, it takes time and energy and patience. And sometimes a friend to help."* Participant 1: "*To affirm yourself and don't rely on external validation or the outcome you're hoping for to determine your worth…And be patient, it takes time for system changes to unfold."* Participant 4: *I would say the key thing is to research and get the statistics, and don't go in combatively."* Participant 5: *"The other thing is I would be straight up front. I think you need to open your realm. A lot of parents just sit there, just expect things to function on their own."*

3) Caregiver relief for positive outcomes

Significant improvements in health were attributed to medical cannabis, and the caregiver's relief for these positive outcomes was evident. Participant 5 said, "*His prescription has been life changing. He is able to now attend school and play with friends… We've had no meltdowns at school, zero. That would be not possible without the cannabis. Not possible.*" According to participant 2, "*We're just most grateful for a less violent kid.*"

Caregivers expressed gratitude for healthcare providers that helped navigate the process. According to participant 3, *"We were lucky enough to have a really amazing pediatrician and that doctor was very receptive."* Participant 4 said *"And it's just by divine intervention, luck, that she [the physician]'s passionate about cannabis and kids. It was fate that we tried it again."* Participant 2: *"And so this gentleman was available to us by email… and I have thanked him and thanked him and thanked him to this day for doing that for us."*

6.5 Discussion

Some children taking medical cannabis require dose administration at school. Since administrative policies to support children taking medical cannabis and their families vary across Canada and some schools prohibit its use altogether [12], we sought to characterize perspectives of caregivers. Except for two parents who faced barriers with medical cannabis administration, most described positive or neutral experiences with the schools. Consistent with our previous study of clinicians who prescribe medical cannabis [7], caregivers encountered a lack of knowledge about medical cannabis within the school system. However, in the present study only 6/12 participants had direct experience with medical cannabis in schools, most because it was dosed twice daily around school hours. Hence, data saturation was not reached and more study on this topic is warranted.

A semi-structured interview process provided flexibility to continue the interview with a focus on medical cannabis in general and saturation was achieved in this domain. The tenacity of participants to advocate for their children was highlighted and the categories of ‘challenges’, ‘parents as advocates’ and ‘caregiver relief for a positive outcome’ remained consistent throughout the cohort. Identifying a suitable authorizer and cost were among the top challenges, which agrees with two recent Canadian studies of parents of children taking medical cannabis for epilepsy (n=19) [6], and cancer and epilepsy (n= 10) [5]. Both studies also describe the relentless pursuit of caregivers to acquire knowledge and navigate the medical system to achieve a positive outcome for their child with a refractory condition.

Our study is unique in that in addition to describing the experiences, we queried caregivers about the facilitators that allowed them to successfully advocate for their child despite significant obstacles. A variety of knowledge, skills, and attitudes were deemed important, such as the ability to synthesize information and keep up to date on cannabis pharmacology, communicate effectively and act as an educator, be proactive and practice resilience. They provided their perspective on what was important for schools and other caregivers to know. The participants in this study were well-educated and articulate and 50% were health care providers; we surmise that caregivers who lack such confidence and self-efficacy – especially within the healthcare system - may not be successful with navigating medical cannabis for their children. Efforts should be undertaken to support all caregivers of children who require medical cannabis, so the burden does not fall exclusively to the family. For example, creating accessible, evidence-based education that could be shared with teachers, families, or friends may help decrease stigma and alleviate the need for caregivers to continuously articulate ‘the science’ behind medical cannabis.

This study has several limitations. We recruited participants by advertising through Canadian websites and social medical channels. Although 30 participants provided contact information, we could schedule appointments only for 12. Selection bias could have played a role, whereby participants who felt confident and strongly about the topic, and had positive experiences with medical cannabis, were more likely to respond to follow-up communications and participate in the study. We set out explore the perceptions of medical cannabis in schools but only 6 participants had direct experience and data saturation was not achieved on this topic, since many medical cannabis regimens are administered on a twice daily basis, negating the need for administration in school hours. Nevertheless, rich dialogue ensued on the experiences of medical cannabis in general. While we aimed to learn from caregivers across Canada, the majority of participants were from Ontario and British Columbia. We acknowledge that regional differences exist and may influence caregiver's experiences with respect to medical cannabis.

6.6 Conclusion

Caregivers demonstrate remarkable tenacity despite the many challenges associated with medical cannabis use, but education and practice change are needed to ensure that children using medical cannabis can benefit from or continue to experience its positive outcomes within the school environment and beyond.

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*More details on study methodology can be found in Appendix A

6.7 References

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CHAPTER 7. DEVELOPMENT OF THE REACH (REAL EDUCATION ABOUT CANNABIS AND HEALTH) PROGRAM

King PM, Klemmer J, Mansell K, Alcorn J, Mansell H. Development of the REACH (Real Education About Cannabis and Health) Program for Canadian Youth. J Nurs Educ. 2020;59:465-469. doi: 10.3928/01484834-20200723-09.

HM, PMK, JK and KM designed and implemented the program. HM drafted the manuscript. PMK, JK, KM, JA critically revised the manuscript, and have approved the final version to be published. HM was the corresponding author.

7.1 Abstract

Background: Because cannabis use in children can have negative consequences, the recent legalization of recreational cannabis for adults in Canada creates an urgent need for youth education.

Method: A multidisciplinary clinical rotation was developed wherein nursing and pharmacy students collaborated with youth (grades 7 through 10) to construct an educational program about cannabis. Four schools participated, representing a variety of socioeconomic demographics. Feedback was solicited from students and stakeholders. The purpose of this project was to create REACH (Real Education about Cannabis and Health), a toolkit and curriculum resource that includes lesson plans for teachers covering the science of cannabis, social science implications, peer pressure, decision making and harm reduction, videos featuring youth testimonials, and supplemental resources.

Results: Preliminary feedback suggests the materials are engaging and informative.

Conclusion: A collaboration of health science students with youth in schools resulted in an authentic and relatable educational program about cannabis. Future studies will evaluate REACH's effectiveness in seven and ninth-grade students.

7.2 Introduction

In October 2018, the *Cannabis Act* (Bill C-45) came into effect. This act federally legalized the recreational use of cannabis for adults in Canada [1]. Lawmakers proposed certain benefits to legalized cannabis, which included the potential for decreased criminal activity through governmental regulation and oversight, the opportunity to generate tax revenues, and a reduction in government expenditures on law enforcement that addressed illegal cannabis consumption [2]. Yet, opponents of cannabis legalization argued that legalized recreational use posed societal risks. The increased access to legal cannabis may potentiate harms in vulnerable populations—pregnant women, children, individuals with low socioeconomic status, or mental illness— increasing both prevalence and consequence of acute and long- term health and behavioral effects of cannabis use [3,4].

In children, the risks of cannabis use are well documented. Long-term frequent cannabis use during brain development may permanently affect attention, memory and learning centers of the brain [5]. Early initiation of cannabis use, i.e., use before the age of 16, is more likely to associate with serious mental health conditions, including psychotic symptoms, schizophrenia, and depression, as well as the risk of suicide [6-9]. Cannabis use before the age of 25 may lead to poor academic performance, a higher likelihood of driving while intoxicated, and an increased risk of dependency [6,8,10].

The prevalence of cannabis use in youth has been consistently high in Canada. Compared with their peers in other developed countries, Canadian adolescents are among the highest rates of cannabis use [11]. Notably, youth between the ages of 15 and 24 years have reported usage rates that are more than double that of adults [12]. Research suggests the younger generation perceives cannabis use to be widespread and often feels indifferent to its potential risks [13]. Such behaviors and attitudes suggest a need for credible, evidence-based information to allow youth to make confident and informed decisions about cannabis consumption [14].

Traditional didactic educational strategies that focus on abstinence often do not resonate with the experiences of youth [15-17]. In Saskatchewan, the school curriculum combines the topic of cannabis with education on illegal substances, yet the traditional message of "just avoid it" now has little relevance in the current context of legalized recreational cannabis. Recognizing this gap in education, we developed REACH (Real Education About Cannabis and Health), a toolkit and curriculum resource for teachers to use within the classroom to educate youth about cannabis. Young people have a right to access accurate, nonjudgmental, evidence-based health information [18]. Through REACH, youth have the opportunity to develop the knowledge, skills, and attitudes to understand and manage themselves in the changing world of cannabis legalization and regulation.

This innovative educational program was developed through a multidisciplinary collaboration of nursing and pharmacy students, middle school and high school students, university faculty, and middle school and high school teachers. This partnership was intentionally formed because collaboration is considered a best practice for addressing a variety of health issues, including health promotion [19]. Credible and authentic prevention efforts in youth is best achieved by involving youth in the creation of educational materials [20]. Community health nurses and pharmacists brought further credibility to development of the REACH resource as these professions are well-respected frontline health care providers widely recognized for their knowledge and roles in health prevention, promotion, and education [21,22].

7.3 The Multidisciplinary Team

The multidisciplinary team consisted of two faculty from the College of Nursing (P.K., J.K.), two pharmacy faculty from the College of Pharmacy and Nutrition (H.M. and K.M.), twelve 4th year nursing students and one 4th year pharmacy student from their respective colleges at the University of Saskatchewan. The participating nursing students were undergoing a community practice placement to fulfill clinical hours as a requirement for their nursing degree. These placements were through the College of Nursing Safe School Health Improvement Project and Safe School Health Initiative (SafeSHIP) or School Health Initiative with Nursing Education (SHINE) Programs. The SafeSHIP and SHINE programs are community-based partnerships between the College of Nursing and two elementary schools and two high schools in Saskatoon. These programs provide an opportunity for nursing students to work within the schools to fulfill clinical hours in the areas of community partnership, capacity building, and community development. The participating pharmacy student was completing a Specialty Structured Practices Experiential Program as a requirement for the pharmacy degree. The association of the pharmacy student with the nursing team provided a novel opportunity for the pharmacy student to practice in a nontraditional setting, and for multidisciplinary collaboration among the students. Each nursing student spent 260 hours in the community practice placement, while the pharmacist student dedicated 200 hours to this project.

The university team members partnered with youth and staffin two middle schools (St. Luke and North Park Wilson) and two high schools (Bishop James Mahoney High School and Tommy Douglas Collegiate). Geographically, these schools provided student representation from both the public and separate school divisions and represented a broad range of socioeconomic demographics. The participating students ranged from grades 7 to 10.

7.4 Program Content

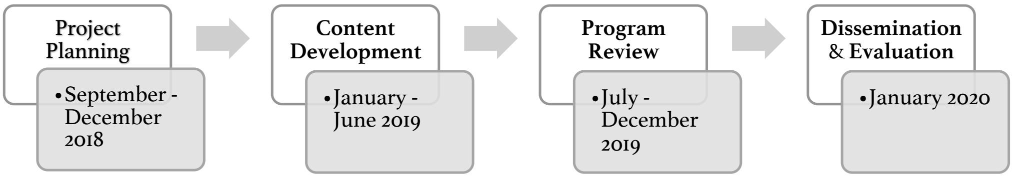
The REACH program consists of two modules, which differ in their content and context based on student age. Module 1 is intended for middle school, and Module 2 is geared toward high school students. Each module consists of four lesson plans which have been mapped to the Saskatchewan Ministry of Education's curricular outcomes and indicators for health education in the seventh and ninth grades, respectively. The four lessons are (a) an introduction to cannabis, (b) the science of cannabis, (c) social science implications, and (d) peer pressure, decision making, and harm reduction. Each lesson lasts approximately 40 to 55 minutes. The modules are adaptable to accommodate a tighter schedule. The REACH program is a curriculum resource that accompanies the modules to help prepare the teacher for a real education about cannabis and health for Saskatchewan youth. The resource includes comprehensive learning outcomes, a list of required resources and materials, directions and lesson outlines, suggested activities, lesson checklists, evaluations, and research highlights. Each module also includes supplementary videos, wherein the participating youth collaborated to share their previous misconceptions and perceptions about cannabis, and why they choose not to use it. Finally, a resource section is provided for teachers to access more information about cannabis to enhance their preparation for the lessons. That appendix includes general information about cannabis, how and why conversations need to take place with youth, cannabis risk reduction strategies, and how to access supports for kids and families. The REACH program used the constructivist approach, embracing and acknowledging the circumstances of both the teacher and learner and encouraging student-centered learning in collaboration with the youth and their peers [23]. The REACH curriculum resource was designed to increase student knowledge about cannabis; nurture protective factors and capacity building in decision making; challenge contextual adaptation skills, confidence, and efficacy in handling future adversities; and encourage the reduction of risks of consumption and social harms. The accompanying illustrations throughout the resources were created by youth within the participating schools. Although the resources were created locally in Saskatchewan, they are sufficiently generic to be shared widely across the country.

The project was funded by the Cannabinoid Research Initiative of Saskatchewan (CRIS), an interdisciplinary research team that aims to obtain scientific evidence about the application of cannabinoids and cannabis derivatives to humans and animals for health, disease, and disorders [24]. Although CRIS is primarily recognized for its research, the group's knowledge translation pillar is committed to improving public awareness about the potential risks and benefits of safe cannabis use, both medical and recreational [25].

7.5 Program Development

REACH's development consisted of four main stages: (a) project planning, (b) content development, (c) program review, and (d) dissemination and evaluation (Figure 7.1). Project planning involved a series of meetings with faculty and teachers, obtaining funding for the project, and logistical development of a framework and timeline.

Figure 7.1 Development of REACH (Real Education About Cannabis and Health)



The content development phase commenced in January 2019 and lasted for 12 weeks during the university students' practical placements. Prior to their interaction with youth in the participating schools, nursing and pharmacy students first developed a fundamental understanding of cannabis, learned best practices for teaching, and developed readiness to answer questions related to cannabis. This required a 2-week immersion into topics such as science and regulations associated with cannabis use; risk and harm reduction; health public policy; promotion, advocacy, and health literacy; developmental theory with a particular emphasis on school-aged children and parents; social competence and peer pressure; decision making and choices; learner and youth engagement; social marketing; and community health nursing standards. The university students consulted with experts to share knowledge and used a collaborative learning model [26]. In the next phase, the university students formed relationships with the teachers and their classes. Consent forms were distributed to the parents, and 195 of 281 consent forms were returned, granting permission for their child to participate. Two separate modules were created to acknowledge differences in cognitive, social, and emotional development among adolescents of various ages [27,28]. One module was used for middle school classrooms (grades 7 and 8), and the other for high school students (grades 9 and 10).

The multidisciplinary team co-developed the program with the cohort of middle school and high school students who contributed extensively to the development of resources in the REACH toolkit. However, resource development required the team to educate the school youth about cannabis. The team created a tentative framework for educating the youth with the understanding that lessons would be adapted as needed based on classroom interactions and engagement. Over the next 10 weeks the university students hosted approximately four face-to-face sessions with each cohort (grades 7 and 8 at St. Luke School, n = 82; grades 7 and 8 at North Park Wilson School; n = 28; grade 9 at Bishop James Mahoney High School, n = 66, and grade 10 at Tommy Douglas Collegiate, n = 19). These sessions consisted of interactive activities to stimulate engagement and discussion, as well as didactic components aimed at meeting the learning objectives established a priori. The teach-back method, shown to be effective in improving comprehension and influencing behavior, was used throughout the lessons [29,30]. After each classroom session, a team debrief—moderated by a nursing faculty member—allowed university students to reflect on what worked well and what could be modified for the next session [31]. Feedback from students and teachers was encouraged and incorporated throughout the process. A professional videographer recorded the sessions. Given its complexity, an animator was hired to provide a visual depiction of how cannabis works in the body.

7.6 Program Review

The university students repeated each session multiple times with new students. Each session was followed by a debriefing, which allowed continual reflection and opportunity to revise and refine the content. Feedback from students and teachers was also encouraged and incorporated throughout the process. After completion of all classroom encounters, the university students and faculty finalized the lesson plans, videos, and other resources, and formatted them for review. The materials were shared with other stakeholders, including additional parents and educators and representatives from the Ministry of Education. Edits were applied accordingly.

7.7 Final Product

The social context regarding cannabis use in Canada is undergoing considerable change. To help address this change, the REACH program provides a curricular resource to help students navigate conversations about cannabis and health. REACH supports student achievement of curricular outcomes by embracing a comprehensive school community health approach; educating the whole person through holistic learning of body, mind, and spirit; focusing on achieving health literacy and efficacy related to cannabis; building inquiry skills; and responding to and addressing community perceptions, norms, and context [32].

7.8 Lessons Learned

Participation in the program's development was an excellent learning experience for the participating youth and teachers and feedback has been positive. One middle school teacher stated:

> *As a teacher of adolescents, I feel that this program should be brought to all Saskatchewan classrooms. This program covers the emotional, physical, and social aspects of cannabis use and the consequences associated with each. I felt that the presentation of the information was geared towards the student's needs, as cannabis use is a reality among today's youth.*

A grade 8 student at one of the participating schools suggested that the program "provided actual, beneficial information to educate adolescents…. Nothing was glossed over or sugar-coated…. It taught us many ways to handle peer pressure when it comes to cannabis use." Our nursing and pharmacy students had the opportunity to be part of a multidisciplinary team and to collaborate, along with teachers and students from the community. Each discipline discovered what they had to offer in this environment, and the nursing and pharmacy students gained experience in role clarification and collaborative leadership within this context. They learned how to build trust and establish a rapport with the youth creating a safe space for honest discussion. According to the feedback, the experience was worthwhile, and the skills developed can be extrapolated to other settings. One nursing student said:

> *As a nurse in training, it was tremendously valuable for me to apply various methods of youth engagement strategies with adolescents. Observing first-hand how approaches like the teach-back-method sparked interest and created learning opportunities will benefit my professional practice for years to come.*

7.9 Conclusion and Next Steps

A collaboration between nursing and pharmacy students with youth in grades 7 through

10 resulted in an authentic and relatable educational program about cannabis. The nursing and pharmacy faculty will work diligently to make the toolkit widely available to schools and teachers across the province. A graduate student at the University of Saskatchewan continues development of a generic tool suitable for assessment in youth to assess youth knowledge about cannabis. The effectiveness of the REACH program on cannabis knowledge retention and behavior intention will be evaluated in a cohort of grade 7 and grade 9 students using pre- and post-design study. To follow our progress, please visit, https://words.usask.ca/cannabised4kids/.

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CHAPTER 8. GENERAL DISCUSSION AND CONCLUSIONS

8.1 Medical Cannabis in Children, Youth and Young Adults with ADHD

The use of medical cannabis for treating chronic conditions in children, youth and young adults remains controversial due to the lack of an evidence base and understanding of appropriate dosing requirements. As a highly prevalent condition affecting over 7% of children and 2% of adults [1,2], the first objective of this dissertation was to examine the treatment efficacy and pharmacokinetics of cannabis in ADHD. Despite the dearth of evidence, the public, through social networks and the grey literature, identifies considerable interest in the possible benefits of cannabis treatment for ADHD [3-6].

Chapter 2 describes a protocol for a mixed-methods proof-of-concept study to objectively assess the treatment efficacy of cannabis in a cohort of patients **already taking** cannabis (at a THC:CBD ratio of 1:20) as a treatment adjunct to stimulant pharmacotherapy, in addition to other medications. A subsequent protocol was also developed for a single dose pharmacokinetic study in a **cannabis naïve** population of children with ADHD to explore its absorption, distribution, metabolism, and elimination. Understanding the impact of pharmacotherapy is of particular importance in the pediatric population, where the developing child may be adversely and unpredictably impacted by drug therapy. Controlled clinical trials are needed to determine the impact of cannabis use on ADHD symptoms since poorly controlled ADHD can be detrimental to the developing child. However, before an interventional study can be attempted, we first need to understand the pharmacokinetics of cannabis in the pediatric patient. Pharmacodynamic and pharmacokinetic processes of absorption, distribution, metabolism, and excretion undergo changes with growth and development, and therefore we cannot assume they can be extrapolated directly from adults [7]. Understanding the nuanced effect that age and development may play on pharmacokinetics is critical to design a dosing regimen for a clinical trial, and these preliminary studies are a necessary first step in this process. Examining the pharmacokinetics in a population already taking cannabis is the safest way to generate initial data. These results can then provide guidance for selecting a dose to further examine pharmacokinetics in a cannabis naïve population with ADHD. Finally, this preliminary work could set the stage for a future clinical trial to explore efficacy. Several challenges occurred which limited our ability to undertake this research, necessitating a shift in direction. A significant amount of time was dedicated to designing the protocol for the single dose pharmacokinetics study. The first draft of this protocol is provided as an appendix because we could not perform the study (appendix B).

Changes to the Original Study Protocol

The Covid-19 global pandemic was a significant barrier which impeded the research. Several amendments were made to the original mixed-methods proof-of-concept study protocol to maximize the chances of success (Appendix C). The initial plan was for the study to take place at the Saskatoon Health Authority. Recruitment would occur during regular clinic visits with the study physician, and the study activities (interviews and blood sampling) would take place during a pre-scheduled study visit at the Saskatoon Health Authority. Amendments to the process were necessary so that the recruitment and study interviews could occur virtually or by phone. The mobile lab was used to collect blood samples at the patient's residence, to minimize the risk of Covid-19.

The inclusion criteria for this study originally consisted of children between the age of 12 and 18. The study physician (DQ) reviewed the charts from his practice and discovered that most of the patients authorized cannabis were 18 or older. An amendment was obtained to include participants up to age 25. As well, patients were advised/authorized by the study physician to obtain cannabidiol oil (THC:CBD 1:20 ratio), but much variation was noted between product, strain and supplier, since the patient is ultimately responsible for obtaining the product. An additional amendment was added to allow for collection of a small sample of the cannabis product and its testing to confirm the cannabinoid composition of the product.

These revisions were approved by the Behavioral Ethics Board at the University of Saskatchewan and are included in the protocol described in chapter 2 and published in *JMIR Protocols.* The term 'medical cannabis' was used throughout the published protocol to remain inclusive of participants who refrained from using the product authorized by the study physician (cannabidiol oil (THC:CBD 1:20) bid, ingested orally from a specific licensed producer). This was done intentially to maximize our enrolment. We acknowledge that cannabis studies are ideally performed with a specific product, standardized dose, dosing interval and method of ingestion and supplier. Consistency is particularly important when undertaking interventional trials.

Enrolment Experiences

The original sample size for the mixed-methods proof-of-concept study was estimated to be 10-20. The study physician reviewed his clinic charts and identified 22 patients who were authorized medical cannabis. However, only eight of the 22 patients who were authorized medical cannabis could provide assent (which was a requirement of the study), thus eliminating patients who had autism spectrum disorder or other cognitive issues, in addition to ADHD. Of the eight potential participants contacted by the study physician, only six agreed to have their contact information passed to the primary researcher (HM). Three patients were willing to participate, but two were not taking the recommended product [cannabidiol oil (THC:CBD 1:20 ratio)]. Another amendment was subsequently submitted to the ethics board so that the research could continue without product exclusion and the results could be shared as a case report. While we unaware of the reasons for non-participation, the possibility of selection bias should be considered (i.e., participants who achieved a positive effect from their medical cannabis may be more likely to participate.)

Cannabis for the Treatment of ADHD, a Report of 3 Cases

Chapter 3 describes a case report of the three individuals who were taking cannabis for the treatment of their ADHD. While clinical trials are preferable for providing insight on drug efficacy, completing the study was not possible. Only three patients were eligible and willing to participate in the study, with two using a different product than the one required in the original study protocol. Our experience reflects many of the challenges that are prevalent with cannabis-based medicine and our study highlighted key barriers with respect to cannabis research.

First, there is tremendous variability amongst cannabis products; therefore, characterizing the pharmacokinetics, dosing, efficacy, and safety is extremely challenging. With around 500 distinct compounds in the leaves and flowering tops of cannabis plants and the ability of soil and climate conditions and cultivation techniques to influence its constituent bioactive components, it is nearly impossible to obtain a consistent product [8]. Cannabis can be inhaled (e.g., smoked, or vaped), taken orally, sublingual or topically; and it comes in a multitude of dosage forms, all of which can influence pharmacokinetics and therapeutic effect [9,10]. The dual supply chain of both medical and recreational cannabis in Canada, provides a unique situation where patients can choose their own cannabis product based on preference, availability, or cost. Taken together, these factors create an unlimited potential for inconsistency.

Second, the high cost of medical cannabis in Canada is a major driver for patients to turn to the recreational marked to access supply. Two of the three patients in our case report obtained their cannabis from a recreational source, and caregivers and clinicians from our qualitative studies echoed significant concerns about the high cost and lack of coverage for medical cannabis. Notably Canada's black market for cannabis has not ceased to exist with the legalization of cannabis [11]. A survey in 2019 conducted by Canadians for Fair Access to Medical Marijuana (CFAMM), the Arthritis Society and the Canadian Pharmacists Association (CPhA), indicated that 37% of people taking medical cannabis were obtaining it from the illegal market [12]. Statistics Canada has confirmed through crowdsourced cannabis prices that the gap price between legal and illegal cannabis is increasing, and in one study, cannabis produced from licensed producers was twice as much per gram compared to the illicit market [13-15]. Some caregivers in our qualitative study described the cost as 'about as high as a mortgage payment per month'. Using an example of a 40 kg child taking a dose of 10 mg/kg/d of cannabidiol oil for the treatment of drug resistant epilepsy [16] we provide a cost comparison between medical and recreational sources using local products and prices. (Table 8.1).

Table 8.1 A local cost comparison of medical and recreational cannabis

	Product	Supplier	CBD content	THC content	Price for 30ml bottle	Price per month
Example: A 40kg child taking CBD:THC (20:1) oil for the treatment of DRE at a dose of 10mg/kg/d	Cannimed CBD oil	Cannimed (medical source)	21.7mg/g (20mg/ml)	<1.6mg/g (0.5-1.5mg/ml)	$54	$1080
	Dosecann CBD oil	The Pot Shack (recreational source)	26mg/g	1mg/g	$19	$380

Licensed producers of medical cannabis must follow Health Canada's Good Production Practices and their products undergo testing to ensure conformance quality. People who use recreational cannabis for a medical use are at risk of untoward effects by using an inconsistent, unregulated product because the chemical composition, potency and quality cannot be guaranteed.

Our experience also highlights the challenges with conducting clinical trials using cannabis. Randomized clinical trials are the gold standard for objective evidence-based data regarding treatment efficacy because of their potential for limiting bias. Clinical trials require a strict inclusion and exclusion criteria and the use of a standardized intervention or exposure, which is especially difficult with cannabis. The lack of a standardized dose and the variation in chemical constituents complicate the exposure significantly [17]. Furthermore, clinical trials require a standardized method of administration that is acceptable to all participants and the creation of a placebo that is identical in taste and smell to promote effective blinding (in the case of a placebo-controlled trial). Clinical trials are time and resource intensive to conduct, and difficult to justify since the results of one cannabis trial are not generalizable to different products and strains. Much of the data to date about cannabis, therefore, is derived from cohort and case-control studies and observational data will continue to be a main source of information [17]. It is highly unlikely that studies will ever be performed with smoked cannabis, rendering observational data even more important with this route of ingestion.

In an area where data is limited, case reports are important for documenting observations and sharing experiences on a subject of study, along with its related contextual conditions [18].

We could only find one trial investigating the efficacy of cannabis in the context of ADHD and two case reports. In the study by Cooper and colleagues, Sativex Oromucosal Spray (1:1 THC:CBD) was titrated and compared to placebo in 30 adults with ADHD at 6 weeks [19]. In the primary intent to treat analysis, there was a pattern of improvement in cognitive performance in the Sativex group (measured by the QbTest) that did not reach statistical significance (Est= 0.17, 95% CI-0.40 to 0.07, p=0.16, n=15/11active/placebo). With respect to secondary outcomes, hyperactivity / impulsivity was improved with the intervention (p=0.03). The effects were higher in the per-protocol analysis [19]. Two case reports also suggested of potential efficacy of cannabis in ADHD; one described an adult male who experienced improvements in performance tests (ART2020 and TAP) while smoking cannabis [20], while another adult male from Finland experienced adverse effects from methylphenidate, but experienced ADHD symptom improvements from taking an oral commercial product high in THC [21]. Given the constraints with cannabis research and the minimal literature, our case report provides a meaningful contribution with detailed personal accounts from three patients and objective evidence of improvement in ADHD symptoms. Interestingly plasma levels of the cannabinoids were not detectable in the trough samples and we can not rule out the possibility of a placebo effect. The absence of detectable plasma levels does not preclude drug efficacy, however, since the precise mechanism of ADHD and pharmacology of cannabinoids remains to be determined. Clearly more investigations are required on this topic. We recommend that whenever possible, clinicians objectively monitor symptoms (i.e., by using validated scales as we have in this case report) in the quest to increase the evidence for cannabis-based medicine. We also suggest that cannabis products be tested for chemical make-up and composition to confirm that patients are receiving what is intended and to provide a context in which to evaluate the results. This is particularly important with unregulated products, as studies have shown that what is listed on the label may not match what is in the product [22,23].

8.2 Medical Cannabis in Schools

In chapters 4,5 and 6 we explored medical cannabis in schools. The concept for these studies originated from the Canadian Collaborative for Childhood Cannabinoid Therapeutics (C4T) Medical Cannabis in Schools working group [24]. An exhaustive review of the literature, and search of Canadian cannabis laws and policy identified only five scientific articles (which were not relevant to the Canadian context), and one school policy on the topic of medical cannabis in schools. A review of Canadian legislation identified inconsistencies amongst the provinces and territories, and a lack of guidance for schools. Qualitative interviews with 13 physicians across Canada who authorize medical cannabis for children corroborated these findings. They shared their perceptions about medical cannabis in schools (and in general), describing challenges such as a lack of knowledge and stigma, and pragmatic challenges, such as finding an appropriate person to administer the cannabis dose during the school day, as well as storage, and other bureaucratic issues. A follow up study with caregivers of children who require medical cannabis (n=13) echoed similar statements. However, since only half of the cohort's children received medical cannabis in schools (usually because a mid-day dose was not required), these caregivers primarily described the challenges of medical cannabis in in general. Categories in this analysis included the role of parents as advocates, their relief for achieving a positive outcome with medical cannabis and their challenges experienced. While these cohorts provided valuable insight, their demographic make up deserves particular attention. We recruited clinicians and caregivers through various Canadian websites and social medical channels which were expected to reach the target audience of clinicians who authorize medical cannabis and caregivers for school-aged children and youth that require medical cannabis. This type of recruitment strategy resulted in a cohort of physicians that felt positive about medical cannabis in general and a group of caregivers who were passionate, affluent and educated; they were also strong advocates for their children. Medical cannabis is a topic with polarizing perspectives and we caution against generalization of these results to other populations.

As in other research [25-27], stigma was cited as a challenge by caregivers and clinicians. Caregivers described situations where they experienced stigma with physicians, school administrators and staff, and/or family. In many situations these perceptions improved over time, after the family member, physician or teacher realized the positive impact cannabis was having on the child's health and quality of life. Nevertheless, the caregivers had to continually advocate for their child to receive the care and level of support that was deserved. To maintain credibility, they were required to remain knowledgeable and up to date on the research regarding cannabis and educate individuals within their circle about the benefits and nuances of medical cannabis. They also described the importance of being effective communicators with health care providers and teachers and having tenacity to *'sustain the journey'* to achieve positive outcomes with medical cannabis. Clinicians attested to the misconceptions about medical cannabis and stigma persisting within in the health care setting. A lack of knowledge about cannabis by health care providers has been also described by others [28-30].

Difficulty in finding an authorizing physician was another major challenge for caregivers. Parents sought out cannabis as a last resort treatment alternative since traditional medications were not adequately meeting their child's needs. However, they were often met with resistance or skepticism when broaching the topic of medical cannabis and were forced to find an alternative physician. Some caregivers had to meet with multiple health care providers to find someone willing to work with them and described this as the biggest barrier with medical cannabis. Likewise, Elliot and colleagues interviewed parents of children with drug resistant epilepsy (n=19) and found that nearly half sought out cannabis authorizations from outside the child's normal circle of care [26].

The high cost of medical cannabis was voiced as a top challenge by nearly all caregivers and most clinicians. For some caregivers the cost amounted to "about a mortgage payment per month". Caregivers and clinicians expressed concern that marginalized families may not be able to afford this treatment. For example, one caregiver said, *"I think there's a very unethical healthcare inequity because it's an uncovered benefit for nearly everybody and the out-of-pocket costs are high, so it's only accessible to those who aren't sort of low on the rank of the social determinants of health."* Issues with obtaining a consistent product and finding the correct dosage were also cited as barriers by caregivers and clinicians, albeit less frequently.

Many of the challenges associated with medical cannabis in Canada are related to the legal framework. The *Cannabis Act* [S.C. 2018, c. 16] created separate medical and recreational streams for purchasing cannabis. Compared to prescription medications, medical cannabis is not required to undergo the same rigorous process to establish pre-market safety and efficacy and is not issued a notice of compliance or Drug Identification Number (DIN) by Health Canada. Medical cannabis is obtained from a licensed producer (versus a pharmacy), and an 'authorization' (versus a prescription) is required to obtain cannabis for medical purposes for individuals under the age of 18. These subtle, yet important differences, contribute to pragmatic challenges because medical cannabis is not truly a 'prescription medication'. For instance, institutional policies that specifically apply to prescription medications do not technically include medical cannabis. Coverage for medications is often formulary based, meaning that insurers will have a 'list' of drugs for which they provide reimbursement. Since cannabis does not have a DIN, it is excluded from drug formularies, and patients often must pay out of pocket for this type of medical treatment. In addition to compounding the challenges with cost, these important distinctions can also contribute to misinformation and stigma.

Moving the Area Forward

Fortunately, nearly all clinicians described improvements over time in their school-related encounters and experiences with medical cannabis in general. Likewise, caregivers alluded to improvements in accessibility and knowledge, perceptions, and stigma. Caregivers and practitioners described how treating medical cannabis like any other medication, improving education, communication, and support for families could help bridge the current gaps with medical cannabis in children.

In theory, medical cannabis should be treated no differently than other medications. However, some jurisdictions have pre-existing policies (or laws) that prohibit the use of cannabis. With its history of recreational use, cannabis may also provoke additional anxiety in the schools' setting. Schools are responsible for the safety and well-being of all students while they are on school property. School boards and/or employees can be held liable in situations where a student's safety is compromised. School boards might be inclined to prohibit medical cannabis because of the potential liability and risk of storing and administering a substance that could be misused. Furthermore, staff may feel that they lack the expertise or time to safely administer medical cannabis to a child. The potential for diversion (medical cannabis that is accessed by students could be shared or sold for recreational use) is another potential risk of storing medical cannabis at school.

Strategies can be undertaken to mitigate these risks. All institutions should have a pre-existing policy that provides guidance for when children need medications. Under such policies, a child who requires pharmacotherapy should have a medication plan providing specific details on who should administer the medications, how and when they are administered, where they are safely stored, and how they are disposed of. Parents are should be required to provide documentation that such medications are authorized by a licensed prescriber (e.g., physician or nurse practitioner), and all doses administered during the school day are recorded on a medication administration record (MAR). The person deemed responsible for administering medications during school hours should be appropriately trained and capable. It should be remembered that other medications sometimes required by children (such as stimulants for the treatment of ADHD, or prescription pain medications) can be abused and similar protocols should be applied. Rules and regulations should be updated to recognize the legitimate role of medical cannabis. Teachers, school administrators, caregivers and parents should work together to identify barriers and create logistically feasible solutions for administering cannabis in schools when medically necessary. Building off existing frameworks and procedures for other controlled medications (e.g., stimulants or benzodiazepines) is a logical place to start for schools that require updated polices to accommodate medical cannabis. A harmonized approach for supporting children that require medical cannabis in schools is recommended across Canada. Countries that are implementing a framework to legalize cannabis should consider such scenarios during policy development.

The clinicians and caregivers we interviewed perceived education to be an important way for decreasing stigma about medical cannabis. From their insights we were able to generate a list of important principles for cannabis education in schools and information that the clinicians and caregivers deemed to be important for teachers and school administrators. Caregivers also provided advice to other families and described the knowledge, attitudes, and skills they perceived to be necessary for achieving positive outcomes with medical cannabis. As a first step in knowledge translation, we are publishing these papers in peer reviewed journals so that pediatricians and other health care providers can learn about these experiences and challenges. We also plan to disseminate this information in lay language formats using strategies tailored for the general public, and other parents of children who require medical cannabis might benefit from these insights.

The C4T Medical Cannabis in Schools working group can use these findings to inform the development of educational materials that can be used in schools. Other ideas for improving the status quo include creating standardized protocols, procedures, or templates for documentation. These resources may be helpful for clinicians who authorize medical cannabis, or teachers and administrators that facilitate cannabis administration in schools. While interviewing clinicians and caregivers was indeed helpful, we acknowledge that other stakeholders are necessary to gain the full perspective on this topic. Incorporating perspectives from teachers and school administrators will be necessary to create relevant and effective resources.

8.3 Recreational Risk Reduction for Children in Schools

The legalization of recreational cannabis in Canada and its impact on children, youth, and young adults requires significant consideration. Just as outdated cannabis policies within the school setting no longer accommodate the needs of Canadian children requiring medical cannabis, education within the schools requires an updated perspective as well [31]. Traditional educational messaging that focuses on only abstinence are ineffective [32,33] and given the increased accessibility with the legalization of medical cannabis, youth require knowledge and skills to make health choices about cannabis use [34]. As a key objective of this dissertation, we created a cannabis risk reduction program that could be widely used in schools, promoting meaningful engagement with youth.

The Real Education About Cannabis and Health (REACH) program is a resource for teachers designed to teach Saskatchewan students about cannabis and health. The comprehensive resource and accompanying toolkit were created collaboratively by nurses, pharmacists, researchers, nursing students, pharmacy students, teachers, community partners and youth to meet the learning needs of Saskatchewan students in the changing context of the legalization of cannabis in Canada. REACH consists of two modules; the first is geared towards grade 7, while the second is aimed at grade 9. Both are linked to Saskatchewan curriculum outcomes for each respective grade. The resources were created using the constructivist approach, which emphasizes the role of the learner and posits that learning is more effective when the knowledge is co-created and the learner is actively involved in the process, rather than taking a passive approach [35]. Patient-oriented research aims to engage with relevant stakeholders, including patients, their caregivers, and families in the research process and to apply the knowledge generated from these multidisciplinary teams to improve healthcare systems and practices [36,37]. With drug education, engagement of youth can contribute significantly to the success of the project [34].

Dissemination of the REACH Program and Future Directions

In 2020, this education program was approved as a curriculum resource by the Ministry of Education in Saskatchewan, and its adoption into Saskatchewan schools continues to grow. It is freely available and accessible to Saskatchewan teachers on the Ministry of Education website [38,39] and our team continues to receive inquiries about the resource. The REACH program will be reviewed and revised as new evidence becomes available about cannabis. Based on our scoping review of policies on medical cannabis in schools and our qualitative study on clinician and caregiver perspectives (chapter 4,5,6) it is evident that education is needed about medical cannabis for children. Clinicians and caregivers suggested it would be ideal to provide education to students and teachers early to minimize stigma. Embedding additional messaging about medical cannabis into the

REACH program is the perfect opportunity for providing a wholesome perspective on the benefits and risks of medical and recreational cannabis in children, youth, and young adults, and will be further explored.

8.4 Conclusions

Selected studies exploring medical and recreational aspects of cannabis use in children, youth, and young adults are described in this dissertation. The treatment efficacy and pharmacokinetics of cannabis were examined in three young adults taking cannabis for ADHD. Improvements in symptoms and quality of life were documented subjectively and objectively, attesting to the need for more study in this area; we hope our published protocol stimulates further research on medical cannabis in ADHD. Cannabis use in schools, both medically and recreationally, was explored. A scoping review of the scientific literature, Canadian policies and laws highlighted the lack guidance and discrepancies. Interviews with clinicians who authorize medical cannabis for school-aged children and caregivers described challenges regarding medical cannabis use and provided guidance for moving this area forward. We also developed an educational toolkit for students, parents, and teachers that can be used in Saskatchewan schools. Education is a key strategy for both decreasing stigma about medical cannabis and for taking a risk-reduction approach for minimizing harms associated with recreational cannabis use in children, youth, and young adults.

8.5 Future Directions

Despite the many challenges that are prevalent with research cannabis, future study is needed to characterize the safety and efficacy of cannabis for the treatment of ADHD. A pharmacokinetic study must be completed in children, youth, and young adults to explore the dynamic processes of ADME. Subjects should be stratified categorically according to age to account for ontogeny. A standardized cannabis herbal extract obtained from a licensed producer should be studied, since an oil-based oral formulation is preferred for administration in children. Based on the limited data available and our case report [40] we suggest testing a product containing both CBD and THC, rather than CBD alone. Our draft protocol presented in appendix B can be used as a starting point for designing this study.

Ideally, data obtained from the pharmacokinetic research would be used to design a dosing regimen that could be studied in a randomized placebo-controlled trial to investigate the safety and efficacy of this product. Realistically, the significant time and resources required, and challenges with recruiting a homogenous population for completing such a trial will be prohibitive. N-of-1 trials, which employ a crossover design to assess the effects of a treatment within a specific subject, could be a more realistic alternative for garnering evidence in this era. These studies, while much smaller in scope, maintain sound methodologic principles, including balanced sequence assignment, blinding, and systematic outcomes measurement [41]. N-of-1 trials have been deemed to be useful in the setting of ADHD, particularly when the results of multiple studies are evaluated systematically in a meta-analysis [42]. We recommend the establishment of a working group to develop a standardized n-of-1 trial protocol for evaluating the safety and efficacy of cannabis in the setting of ADHD. A pan-Canada collaborative approach is ideal for this initiative to mitigate the challenges of single center recruitment and to facilitate data pooling to advance the evidence in this area.

Our scoping review and qualitative interviews with clinicians and caregivers identified key areas for supporting patients and families that require medical cannabis in schools. An upcoming C4T Medical Cannabis in Schools Working Group meeting is scheduled to establish concrete next steps. Knowledge translation strategies will be undertaken to disseminate our findings to health care providers, patients and families, the public and policy makers, sharing the experiences and challenges in this population. Developing standardized educational materials that can be provided to schools, as well as a medication policy template and a suggested procedure for administering medical cannabis in schools, could help decrease stigma and improve support for families, teachers, and administrators. These resources, which will be created in collaboration with relevant stakeholders, could help bridge the current gaps with medical cannabis in children.

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Appendix A. Additional details about the qualitative methodology

Since the description of our qualitative of methodology was constrained by the publishing journal's limited word count, a more fulsome discussion is provided in this appendix.

Qualitative description was the methodology we used for the clinician and caregiver studies described in chapter's 5 and 6, respectively. This approach was appropriate as it is a pragmatic and flexible process that does not transform the data beyond recognition [1]. In our case, we wanted to describe the experiences of clinicians and caregivers and to present the data in a format that resembled the research question. For data collection, we opted to conduct semi-structured virtual interviews as they allowed us to complete the research during the Covid-19 pandemic. The semi-structured format ensured that we followed a consistent pattern throughout the dialogue, yet allowed for flexibility to deviate from the script depending on the direction and nature of the discussion. This approach was particularly helpful for discussing the use of medical cannabis in schools; in situations where the participants had little experience with the school context, we were able to shift the discussion to explore the experiences of medical cannabis in general. The interviews for each study were conducted by one individual to maintain consistency throughout the sample (H.M. conducted the interviews with the clinicians and Z.Z. conducted the caregiver interviews).

Data analysis was conducted using qualitative content analysis, since the intent was to remain close to the data, preserving the descriptive testimonials and avoiding overinterpretation or abstraction. While the process for analysis was similar for each study, each was treated as an independent process. Data analysis for the clinician study was conducted during the Fall of 2021, while the caregiver analysis was conducted early in 2022. In both studies, the transcripts (which were transcribed verbatim) were uploaded into the Dedoose program for qualitative analysis [2] and at least two reviewers performed the analysis. (H.M, and Z.Z. analyzed the caregiver interviews and H.M., S.M. and P.M.K. analyzed the clinician interviews). Since studies were undertaken with researchers from multiple centers, we used Dedoose, which facilitated our remote working process consistently and seamlessly. The data analysis process was collaborative and iterative and discussions within the group were held in a virtual room on an as needed basis.

As the first step, the researchers thoroughly reviewed the transcripts in their entirety. The second pass through the data involved labelling sentences and statements with meaning units. Throughout the organization phase, open coding was used to label the meaning units and the codes were organized into categories and sub-categories. Each researcher was assigned a set of transcripts, and they worked tandemly on this process, meeting every couple of transcripts to cross-review and reflect on each other's coding. This resulted in multiple attempts to relabel, refine and reorganize the codes. We found it beneficial to include the interviewee (as one of the coders) in this process as they could provide context of the discussion to the second coder on an as needed basis. Once the transcripts were coded, the group met multiple times to reflect on the dataset as a whole and to map out the codes and categories and discuss outliers. More refinements occurred based on these discussions and consensus occurred naturally, without the need for a third-party reviewer. The results were co-written by the researchers that performed the analysis for each respective study.

Trustworthiness of the data was deemed to be a priority of the group. To maintain credibility, we used a reflexive process which involved multiple coders and sessions for debriefing throughout the analysis. The participants were provided with an opportunity to review and revise their transcript and to comment on the final report. We also used several participants quotes throughout the report. Since the word count was limited for the manuscript, we provided supplementary tables to showcase additional quotes. Providing specific details about our study population and study context enhanced the transferability of the research and following a standardized process for reporting (e.g., the COREQ checklist) [3] helped to maintain dependability. We had multiple investigators with experience in qualitative research collaborate throughout the process and we maintained a documented audit trail (which included iterations of the interview guide, notes from the interviews, team meetings and analytical process). We also maintained a shared research folder for documents pertaining to our research process. These strategies were used to achieve confirmability.

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Appendix B. Ethics approvals

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB) 23/Mar/2020

Certificate of Approval

Application ID: 1726

Principal Investigator: Holly Mansell

Department: College of Pharmacy and Nutrition

Locations Where Research Activities are Conducted: University of Saskatchewan, Canada

Student(s):

Funder(s): College of Pharmacy and Nutrition

Sponsor: University of Saskatchewan

Title: Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder With Oppositional Defiant Disorder

Protocol Number:

Approved On: 19/Mar/2020

Expiry Date: 18/Mar/2021

Approval Of:

* ADHD Consentassent Form.combined. revision.mar
* ADHD study 1- assessent SOP
* Interview guide ADHD.mar.revision.v2
* scaredchild1
* scaredparent1
* depression_patient_health_questionnaire.v2
* SNAP_IV_Long_with_Scoring
* tool_phq9
* cannabis side effect survey

Acknowledgment Of:

* Biomedical Application - ADHD Study.mar.revisions
* Bio 1726 NER (FB)revisions hm

Review Type: Full Board

Meeting Date: 15/Jan/2020

IRB Registration Number: Not Applicable

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CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal risk projects at a full-board (face-to-face) meeting. If a project has been reviewed at a full board meeting, a subsequent project of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2018).

Digitally Approved by Dr. Gordon McKay, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB) 03-Feb-2021

Certificate of Approval Amendment

Application ID: 1726

Principal Investigator: Holly Mansell

Department: College of Pharmacy and Nutrition

Locations Where Research Activities are Conducted: Participant's home, Canada

Student(s):

Funder(s): College of Pharmacy and Nutrition

Sponsor: University of Saskatchewan

Title: Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder With Oppositional Defiant Disorder

Protocol Number:

Approved On: 28-Jan-2021

Expiry Date: 18-Mar-2021

Approval Of:

* Biomedical Application Form_ADHD Study v2
* ADHD Study 1_Assent SOP Jan 2021 v2
* ADHD Consent Assent Form Combined v2
* Safe Research Plan_Ethics 1726

Acknowledgment Of:

* Biomedical Amendment Form_Jan 2021
* Reviewed with COVID-19 safety considerations in mind

Review Type: Delegated Review

IRB Registration Number: Not Applicable

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal projects at a full-board (face-to-face) meeting. If a project has been reviewed at a full board meeting, a subsequent project of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2018).

Digitally Approved by Dr. Gordon McKay, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB) 24-Feb-2021

Certificate of Re-Approval

Application ID:	1726
Principal Investigator:	Holly Mansell
Department:	College of Pharmacy and Nutrition
Locations Where Research Activities are Conducted:	Participant's home, Canada
Student(s):	
Funder(s):	College of Pharmacy and Nutrition
Sponsor:	University of Saskatchewan
Title:	Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder With Oppositional Defiant Disorder
Approval Effective Date:	18-Mar-2021
Expiry Date:	18-Mar-2022
Acknowledgment Of:	
Review Type:	Delegated Review
IRB Registration Number:	Not Applicable

* This study, inclusive of all previously approved documents, has been re-approved until the expiry date noted above

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal projects at a full-board (face-to-face) meeting. If a project has been reviewed at a full board meeting, a subsequent project of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2018).

Digitally Approved by Dr. Gordon McKay, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB) 30-Apr-2021

Certificate of Approval Amendment

Application ID: 1726

Principal Investigator: Holly Mansell

Department: College of Pharmacy and Nutrition

Locations Where Research Activities are Conducted: Participant's home, Canada

Student(s):

Funder(s): College of Pharmacy and Nutrition

Sponsor: University of Saskatchewan

Title: Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder With Oppositional Defiant Disorder

Protocol Number:

Approved On: 24-Apr-2021

Expiry Date: 18-Mar-2022

Approval Of:

* Notice of Ethical Review Response, rec'd 22-Apr-2021
* Biomedical Amendment Form, rec'd 13-Apr-2021
* Biomedical Application, Prospective, rec'd 13-Apr-2021
* Participant Information and Consent Form, Version 3, March 2021

Acknowledgment Of:

Review Type: Delegated Review

IRB Registration Number: Not Applicable

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal projects at a full-board (face-to-face) meeting. If a project has been reviewed at a full board meeting, a subsequent project of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2018).

Digitally Approved by Dr. Gordon McKay, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan

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UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB) 15-Jul-2021

Certificate of Approval Amendment

Application ID: 1726

Principal Investigator: Holly Mansell

Department: College of Pharmacy and Nutrition

Locations Where Research Activities are Conducted: Participant's home, Canada

Student(s):

Funder(s): College of Pharmacy and Nutrition

Sponsor: University of Saskatchewan

Title: Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder With Oppositional Defiant Disorder

Protocol Number:

Approved On: 14-Jul-2021

Expiry Date: 18-Mar-2022

Approval Of:
* ADHD Consentassent Form.combined.v4
* Biomedical Application - ADHD Study.v4

Acknowledgment Of:
* Biomedical Amendment Form
* Reviewed with COVID-19 safety considerations in mind

Review Type: Delegated Review

IRB Registration Number: Not Applicable

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal projects at a full-board (face-to-face) meeting. If a project has been reviewed at a full board meeting, a subsequent project of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2018).

Digitally Approved by Dr. Ildiko Badea, Ph.D.
Vice-Chair, Biomedical Research Ethics Board
University of Saskatchewan

UNIVERSITY OF SASKATCHEWAN

Behavioural Research Ethics Board (Beh-REB) 22-Jul-2021

Certificate of Approval

Application ID:	2804
Principal Investigator:	Holly Mansell
Department:	College of Pharmacy and Nutrition
Locations Where Research Activities are Conducted:	Saskatoon, SK, Canada
Student(s):	
Funder(s):	
Sponsor:	University of Saskatchewan
Title:	Medical cannabis in schools: The experiences of caregivers and clinicians
Approved On:	22-Jul-2021
Expiry Date:	22-Jul-2022
Approval Of:	Behavioural Research Ethics Application Study Advertisement Invitation Letters Initial Contact Form Consent Form Interview Guide
Acknowledgment Of:	
Review Type:	Delegated Review

CERTIFICATION

The University of Saskatchewan Behavioural Research Ethics Board (Beh-REB) is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TPCS 2 2018). The University of Saskatchewan Behavioural Research Ethics Board has reviewed the above-named project. The proposal was found to be acceptable on ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to the conditions outlined in the original protocol submitted for ethics review. This Certificate of Approval is valid for the above time period provided there is no change in experimental protocol or consent process or documents.

Any significant changes to your proposed method, or your consent and recruitment procedures should be reported to the Chair for Research Ethics Board consideration in advance of its implementation.

ONGOING REVIEW REQUIREMENTS

In order to receive annual renewal, a status report must be submitted to the REB Chair for Board consideration within one month prior to the current expiry date each year the project remains open, and upon project completion. Please refer to the following website for further instructions: https://vpresearch.usask.ca/researchers/forms.php.

Digitally Approved by Stephanie Martin
Vice-Chair, Behavioural Research Ethics Board
University of Saskatchewan

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Appendix C. Protocol for a single dose pharmacokinetic study of oral cannabis herbal extract (THC:CBD, 1:20) in children with ADHD. (Draft 1, Sept 2019)

TRIAL OBJECTIVES AND PURPOSE

Primary Objective

1. To characterize the area under the plasma concentration between 0 hour and last quantifiable timepoint ($AUC_{(0\text{-tlast})}$) and maximum concentration (C_{max}) of CBD and THC and their respective psychoactive metabolites when administered as a single dose in children with ADHD.

Secondary objectives

1. To evaluate the safety and tolerability of *Cannabis* herbal extract in children with ADHD.
2. To assess the relationship between patient age, and PK parameters.
3. To determine whether PK parameters of *Cannabis* herbal extract in children are associated with other demographic variables (ex. ethnicity, weight, gender, pharmacotherapy with a stimulant).

Study design

Prospective, open-label, single centre, Phase 1 single oral dose PK study to evaluate the PK of CBD and Δ^9-tetrahydrocannabinol (THC) and active metabolites in paediatric patients with ADHD. Measured metabolites will include 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH THC) and 7-OH-cannabidiol, as well as other major bioactive cannabinoids (e.g. cannabichromene (CBC), Cannabivarin (CBVN)) in medical *Cannabis* oil preparations.

Study Population

At least 16 and 24 participants will be recruited from Dr. Quinn's pediatric psychiatry practice at the Saskatchewan Health Authority. Participants will be between ages 6-18. Children will be stratified into one of 2 groups based on their age (middle childhood 6-11 years old and early adolescence 12-18 years old) as defined according to the NICHD Pediatric Terminology (Williams et al, 2012). We will aim to recruit at least 8 participants in each age group.

Inclusion criteria:

- Children 6 - 18 years of age with a diagnosis of ADHD based on Diagnostic and Statistical Manual of Mental Disorders (5th edition) (APA, 2013).
- Subjects who have permission to participate in the study and are able to adhere to the study conditions (ability to stay 13 h in the paediatric clinical trial unit and to return to the unit daily for 5 days for blood sampling, totally 7 visits.)
- Subjects who are deemed safe to participate by the study physician
- Subjects receiving stimulant pharmacotherapy

Exclusion criteria:

- Any known allergy or intolerance to *Cannabis*
- Previous *Cannabis* use within the preceding 2 months (Participants who have previously used a *Cannabis*-based therapy may be included if they have a 2-month period without use of *Cannabis*-based therapy prior to enrolment in the study)
- Altered hepatic function
- Low albumin
- Bleeding disorder
- On ketogenic diet
- Any unstable medical conditions (such as clinically significant cardiovascular, cerebrovascular, renal, hepatic, gastrointestinal, pulmonary, immunological/oncological, dermatological, hematological, endocrine, neurological, or psychiatric disease, or any other condition) that may have jeopardized the safety of the participant or the validity of the study results as deemed by the study physician.
- Use of psychotropic medications with serotonergic activity (*e.g.* Selective Serotonin Reuptake Inhibitors, Tricyclic Antidepressants, Atypical Neuroleptics).
- Use of any medication known to interact with medicinal *Cannabis* within one week of the proposed study.
- Inability of study participants to attend and complete all study visits.

Medications /Treatments Permitted During the Trial

Stimulant pharmacotherapy (dextroamphetamine, lisdexamfetamine, methylphenidate, mixed salts amphetamine) is first line therapy for the treatment of ADHD (AAP, 2011) and is permitted in this study. Although it is plausible that these medications may interact with the *Cannabis* herbal extract used in this study (increasing sympathiomimetic effects), we will maintain the participants on their current drug therapy for the duration of the study. We believe that the potential role of *Cannabis* in the treatment of ADHD is primarily adjunctive and our aim is, therefore, to study the combination of *Cannabis* herbal extract with stimulant medications.

Cannabis could potentially inhibit the elimination of drugs that are metabolized by CYP2C19 or CYP3A4, and/or its elimination may be inhibited by CYP2C19 or CYP3A4 inhibitors. A pharmacodynamic interaction may occur with other medications such as central nervous system depressants or anticholinergic effects (such as increased drowsiness). These types of interactions are less likely to occur, however, since we are using product high in CBD. Since this is a single dose study, in most cases, it is unlikely that these potential drug-drug interactions would lead to clinical relevance. Nevertheless, all medications must be documented and approved by the study team prior to the study.

The use of psychotropic medications with serotonergic activity (*e.g.* Selective Serotonin Reuptake Inhibitors, Tricyclic Antidepressants, Atypical Neuroleptics) will be prohibited.

Other medications will be assessed on a case-by-case basis. Depending on the drug and the dose, and if perceived to be in the best interest of the patient, the study team may opt to exclude the patient from participation. A list of potentially interacting medications is found in table 2.

Participants will not be permitted to consume alcohol or tobacco or to take over-the-counter medications during the study.

Table 2: Examples of pharmacokinetic or pharmacodynamic drug interactions

Type	Examples	Potential Interaction
Substrates of CYP 2C19	SSRIs (e.g. sertraline, escitalopram, fluoxetine), diazepam, clozapine, ariprazole, modafinil	Pharmacokinetic: cannabis may increase plasma levels of the concurrent drug
Substrates of CYP 3A4	cyclosporine, tacrolimus, carbamazepine, methylprednisolone	Pharmacokinetic: cannabis may increase the plasma levels of the concurrent drug
Inhibitors of CYP 2C19	amiodarone, cimetidine, cotrimoxazole, metronidazole, fluoxetine, fluvoxamine, fluconazole, and voriconazole	Pharmacokinetic: plasma levels of THC, CBD or other metabolites may be increased by co-administration
Inhibitors of CYP 3A4	ketoconazole, clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, voriconazole, and boceprevir	Pharmacokinetic: plasma levels of THC, CBD or other metabolites may be increased by co-administration
Inducers of CYP 2C19	rifampin, barbiturates, carbamazepine, phenytoin	Pharmacokinetic: plasma levels of THC, CBD or other metabolites may be decreased by co-administration
Inducers of CYP 3A4	rifampin, barbiturates, carbamazepine, phenytoin	Pharmacokinetic: plasma levels of THC, CBD or other metabolites may be decreased by co-administration
Drugs with sympathiomimetic activity	amphetamines (e.g. dextroamphetamine, other ADHD medications)	Pharmacodynamic: May increase tachycardia or hypertension associated with cannabis (additive effects)
CNS depressants	benzodiazepines, (e.g. lorazepam, diazepam) barbituatates (e.g. phenobarbital)	Pharmacodynamic: May increase drowsiness or ataxia associated with cannabis (additive effects)
Anticholinergics	antipsychotics (e.g. haloperidol, quetiapine, olanzepine) diphenhydramine	Pharmacodynamic: May increase tachycardia or drowsiness associated with cannabis (additive effects)

Pharmacokinetic endpoints

Blood samples will be collected for PK analysis at baseline (0 h) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h. There is no standard guideline in the frequency of blood sampling in children, and the number of samples varies with the research question (Altamimi et al, 2016). A single dose of (oral) CBD in humans has a half-life of 1-2 days, therefore we will be extending the sampling to 120 hours (at least five plasma half-lives) to ensure that we are able to fully characterize the elimination phase. This will allow for adequate estimation of the terminal log-linear phase rate constants and AUC extrapolated to infinity, both of which are necessary for the Cl_s/F and V_d/F estimation. Blood samples (1 mL each) will be collected into BD Vacutainer® Barricor™ tubes (Vuong et al, 2017) and will be centrifuged at 2000 x g for 5 minutes to separate plasma. Samples will be subsequently transferred to Eppendorf™ Protein LoBind microcentrifuge tubes and stored at -80°C until analysis. Plasma concentrations of cannabinnoids and metabolites (THC, CBD, 11-OH-THC, 7-OH-CBD, CBC, Cannabinol (CBN), Cannabivarin (CBVN), 11-nor-9-carboxy-tertrahydrocannabinol (THC-COOH) will be determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Fortunately, this method, which is described below, has been previously developed and validated within our institution (Vuong et al, 2018) according to FDA guidelines (FDA, 1998).

Single dose PK parameters will be determined based on plasma concentrations over time. Individual PK parameters will be determined by non-compartmental methods using GraphPad Prism. The following PK parameters will be determined: maximum concentration (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$) log-linear terminal phase rate constant (λ), oral clearance (Cl_s/F), apparent volume of distribution (V/F), and area under the plasma concentration versus time curve ($AUC_{0-\infty}$). Weight normalized (by kg) Cl_s/F, V_d/F, and AUC_{last} will also be determined.

Safety endpoints

The current study will observe the safety of a single dose of *Cannabis* herbal extract given to children with ADHD. It is not expected that the current investigation will be sensitive to detect new or uncommon safety events associated with administration, however, given that very few controlled studies have examined cannabidiol administration to a pediatric cohort, carefully monitoring of adverse effects is warranted. Vital signs including temperature and respiratory rate, as well as an electrocardiogram (ECG) will be performed at periodic intervals throughout the study, (i.e. around the 4-5 hour timepoint where the C_{max} of CBD is expected to occur) (Taylor et al, 2018). A study diary will be given to caregivers and participants to record specific events that may occur throughout the study. A *Cannabis* side effect survey will be administered during the study period. (See also risks related to *Cannabis* in Trial Procedure section below).

Rationale for dose and formulation

While *Cannabis* is available in several dosage forms and can be given by various routes of administration, we will be using a single dose of *Cannabis* herbal extract of 1:20 THC:CBD (purchased from CanniMed® Therapeutics Inc. (Saskatoon, SK)). The dose will be calculated based on the participant's body weight, and a dose of 8 mg/kg CBD equivalents will be used. The product and dose were chosen to be consistent with the Cannabidiol in Children With Refractory Epileptic Encephalopathy (CARE-E) study which is currently ongoing in our institution and in others (Reithmeier et al, 2018). As mentioned, an immense amount of variation can exist between *Cannabis* strains. Keeping this product consistent by using a single producer and providing the same since dose that is used in the CARE-E study (Reithmeier et al, 2018), will allow for meaningful comparisons between the two cohorts.

***Cannabis* storage**

The study drug will be stored at controlled temperature at the Royal University Hospital Clinical Trials Pharmacy. It will be locked up until it is accessed by the study physician on the day of the study.

TRIAL PROCEDURES

Procedures to be performed at each visit are summarized in Table 2. It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator. Additional evaluations/testing may be deemed necessary by the investigator and for reasons related to subject safety.

Trial procedures should be completed as close to the prescribed/scheduled time as possible. Any non-scheduled procedures required for urgent evaluation of safety concerns will take precedence over all routine scheduled procedures.

Subject Recruitment and Screening

Potential participants will be identified by the study physician (Dr. Declan Quinn) through his pediatric psychiatric practice. The caregivers of the potential participant will be contacted directly at a clinic appointment or by telephone by the study physician or designate. If the response is positive, a copy of the consent will be provided to the potential participant for review either in the clinic or mailed to their home. Minors who are able to provide assent will be provided with all study information. The potential participant or caregiver will be advised that they can contact the study principal investigator or sub-investigators to request further information regarding the study. Potential participants will be provided with at least a week to decide if they would like to participate, after which time a follow-up phone call will be made by one of the investigators or the study nurse. All study procedures will take place at the Royal University Hospital.

Visit 1 (Pre-study Screening)

Participants will be reviewed for eligibility on their initial in person visit (Visit 1) (see inclusion and exclusion criteria). If eligible, and the caregiver and participant indicate that they would like to participate, written consent / assent will be taken and documented. Participants will be then scheduled for their first dosage visit (Visit 2).

The following procedures/assessments will be performed during the screening and reviewed by the study physician:

- Obtain and document verbal informed consent/assent
- Past medical history review, document comorbidities
- Height and weight (to approximate the subject's dose of the study drug)
- Eligibility review
- Document sex, age and race/ethnicity
- Medication review
- *Cannabis* side effect survey (Sexton et al, 2019)
- SNAP-IV (90-item) rating scale (both child and caregiver) (Swanson et al, 1983)
- The Screen for Child Anxiety Related Emotional Disorders (SCARED) rating scale (Birmaher et al, 1999).
- Patient Health Questionnaire (PHQ-9) (Kroenke, 2001).

The investigator(s) will complete an eligibility review documenting, in the source notes, the investigator's assessment of each screened subject with respect to inclusion and exclusion criteria. The investigator will maintain a Subject Screening and Enrolment Log. Subjects who fulfill eligibility criteria will be scheduled for the study (visit 2).

Visit 2

Written informed consent and assent will be obtained from caregivers and subjects who are deemed eligible and elect to participate in the study. The consent form will be signed before any study medication is given. A copy of the signed and dated consent form will be given to the caregiver and subject before participation in the trial. The informed consent will adhere to institutional review board (IRB) requirements, applicable laws and regulations. Subjects will be asked to fast from food and drink, except water, for at least 10 hours prior to study medication. Subjects will report to the study location in the morning.

The following procedures/ assessments will be performed:

- Obtained written informed consent
- Medical history
- Concomitant medication review
- Physical examination including height and weight
- Vital signs
- Temperature and respiratory rate
- Urine β-hCG (females of reproductive potential)
- Urine drug screen
- Electrocardiogram (EEG)
- Auditory Continuous Performance Test

Subjects will receive an appropriate volume of the *Cannabis* herbal extract based on the participant's body weight after an overnight fast of at least 10 hours. Children may drink water throughout the fasting period if needed. The dose will be administered using a calibrated syringe followed by 250mL of water to wash down the residual extract from the mouth. Fasting will continue for 1-hour post-dose. The time of administration will be 0 hour. Blood draws for THC, CBD and metabolite assays will be performed at specified time points. Subjects will receive standardized meals at specific time points.

Participants and their caregivers will be offered the choice of receiving an indwelling peripheral catheter for serial blood collections for the first 12 hours of the study, instead of peripheral pokes. Insertion of the peripheral catheter and all blood draws will be performed by a trained phlebotomist or study nurse. We will abide by pediatric recommendations that not more than >3.8% (3 mL/kg) of the total blood volume should be withdrawn at once time (Altamimi, 2016). Various activities (e.g., videos, reading, arts and crafts, and games) will be offered to participants and a recreational therapist will be hired to entertain the children for the 12 hours they must remain at the clinic.

At 1 hour post dose, a standardized breakfast will be provided. *(Waiting any longer for breakfast may be difficult for a child after an overnight fast).*

At 2 hours post-dose, the following procedures/ assessments will be performed:

- Physical examination
- Vital signs
- Temperature and respiratory rate
- Auditory Continuous Performance Test

At 4 hours post-dose:

- A standardized lunch will be provided between the 4th and 5th hour

At 8 hours post-dose, the following procedures/ assessments will be performed:

- Auditory Continuous Performance Test

At 12 hours post-dose, the following procedures/ assessments will be performed:

- Auditory Continuous Performance Test

After the 12-hour blood draw, the participant will be free to go home.

Visits 3 through 7

- The subjects will return to the clinical trial unit to have the blood samples taken at 24, 48, 72, 96 and 120 hours (visits 3 through 7, respectively). An Auditory Continuous Performance Test will be repeated at 24 hours. A follow-up exit interview will be performed by one of the investigators after the final blood draw, and the adverse event diary will be collected. An EEG will be performed.

Procedures for enrolment of eligible subjects

Subjects will be enrolled into the study if they fulfill the inclusion criteria and do not violate the exclusion criteria.

Prior and Concomitant Medications Review
The investigator or qualified designee will review prior medication use and record prior medication taken by the subject within 4 weeks before starting the trial. All medications, if any taken by the subject from the screening visit until the post-trial visit will also be recorded.

Table 3. Study Visit Schedule

Study Procedures	Pre-study[a]	Pre-dose[b]																
	Visit 1	Visit 2												Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
		Study day 1												Study day 2	Study day 3	Study day 4	Study day 5	Study day 6
				Hours (zero hour is the study drug administration)														
			0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24	48	72	96	120
Written Informed consent/Assent		X																
Inclusion/Exclusion	X																	
Medical History	X	X																
Self-report symptom assessments	X																	
Physical Examination[c]		X							X									X
Body Weight and Height[d]	X	X																
Vital Signs (HR, BP)[e]		X							X									
Temperature/Respiratory Rate		X							X									
Urine drug screen[f]		X																
Pregnancy test[g]		X																
Electrocardiogram[h]		X							X									X
Continuous Performance Test[i]		X							X				X	X	X				
Clinic Admission		X																
Clinic Discharge[j]															X				
Cannabis extract administration[k]			X															
Blood for cannabidiol PK[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized meals[m]							X				X								
Adverse events[n]	X																		X
Concomittant medications[o]	X	X																	
Exit interview[p]																			X

[a]Pre-study screening to determine eligibility will be performed within the 3 months prior to dosing with study medication
[b] Pre-dose evaluations can be done up to 24 hours pre-dose at the discretion of the investigator except where noted
[c] Physical exam will be performed pre-dose on Day 1 and post-dose at 4,6 and 12 hours. The pre-dose exam may be performed up to 24 hours prior to dosing
[d] Height and weight will only be done prior to dosing
[e] Subjects must be semi-recumbent for at least 10 minutes prior to having vital signs measured
[f] A urine drug screen Screen includes the following drugs/drug metabolites: 7-amino-Clonazepam; 7-amino-Flunitrazepam; alpha-Hydroxy-Alprazolam; Alprazolam; Amphetamine; Benzoylecognine; Clonazepam; Cocaine; Codeine; Des-alkyl-Flurazepam; Diazepam; Diphenhydramine; EDDP (methadone metabolite); Fentanyl; Flunitrazepam; Flurazepam; Gabapentin; Hydrocodone; Hydromorphone; Ketamine; Lorazepam; MDA; MDEA; MDMA; Meperidine; Methadone; Methamphetamine; Methylphenidate (Ritalin); Morphine;

Nordiazepam; Norfentanyl; Normeperidine; Oxazepam; Oxycodone; PCP; Pseudoephedrine; Ritalinic Acid (Ritalin metabolite); Temazepam; THC-COOH (cannabinoids); Triazolam; Children on treatment for ADHD may test positive for amphetamines
[g] ONLY for females of childbearing potential
[h] An electrocardiogram (EEG) will be performed prior to dosing and with the last assessment
[i] An auditory continuous performance test (CPT) will be performed prior to dosing, and at 2, 8, 12 and 24hours post dosing
[j] Subjects will be discharged at 12H post study drug administration, remainder of blood samples will be obtained on a non-confined basis
[k] AM dose of cannabidiol herbal extract will be administered at 0H with approximately 240mL of water
[l] PK sampling will be performed as close to the time point as possible. The exact time will be recorded.
[m] Breakfast will be served approximately 1hour post-dose, lunch will be served approximately 5 hours post-dose.
[n] Adverse events will be collected from the time of informed consent through to the time of the exit interview (approximately 5-days after the last dose of study medication).
[o] All medications (both prescription and OTC) taken from the time of informed consent through to the time of the exit interview (approximately 5-days after the last dose of study medication) will be collected.
[p] An exit interview will be completed (approximately 5 days after the last dose of study medication).

TRIAL RESTRICTIONS

Diet and Fruit Juice Restriction

Subjects must fast from food and drinks with the exception of water for 10 hours prior to the cannabidiol herbal extract dosing (Visit 2). Standardized meals will be provided during the day of drug dosing at the study location. CBD is highly lipophilic and when administered with a high-fat meal, bioavailability may be increased four-to-five fold (Taylor et al, 2018).

Subjects will refrain from consumption of grapefruit juice, grapefruits and grapefruit products beginning approximately 2 weeks prior to the study day, throughout the trial and until the last blood sample is taken. This is because grapefruit and grapefruit juices may inhibit CYP3A4, and therefore consuming these products may increase CBD plasma levels.

Alcohol Restriction

Alcohol consumption must be avoided throughout the duration of the trial.

Smoking Restriction

Subjects must continue to avoid smoking throughout the trial, until the last blood sample is taken.

Activity Restrictions

Subjects will avoid unaccustomed strenuous physical activity (i.e., running, bicycling, etc.), throughout the trial, until the last blood sample is taken.

Contraception and Pregnancy Testing

Sexually active female subjects of childbearing potential will be tested for urine β-human chorionic gonadotropin (HCG) prior to the study. If positive, the subject will not be enrolled in the trial.

Standardized Meals

Meals (breakfast, and lunch) will be provided to subjects during the admission days. The breakfast will be provided at approximately 1 hours after they study drug dose. Lunch will be provided at approximately 4 hours post cannabidiol dose respectively. The caloric content and macronutrient composition of meals will be the similar for all subjects.

POTENTIAL RISKS

Risks in this study are related to the blood collections and to administration of cannabidiol oil. The risks of blood draws are minimal and include pain, bleeding, infection, bruising, and fainting. The participants will be thoroughly informed of the risks of the procedures through the consenting process and in communication with the Investigator and other study staff. Qualified personnel will be performing the procedures for this study and this should minimize overall risk to participants.

The potential risks related to blood collections

Each participant will choose to have the having blood collected by single needle pokes each time or by having a peripheral intravenous catheter inserted into their arm. The catheter is preferred by the research team. If this option is chosen, it will be inserted by a trained nurse or phlebotomist for ease of drawing blood for the first 12 hours of the study. For the additional time points (24, 48, 72, 96, and 120), a regular needle will be used to collect blood.

The risks of drawing blood by a catheter which is left in the vein for more that 24 hours include: bleeding from the site where the tube is inserted, bruising and local infection with swelling. Rarely, severe infection of the heart valves or bloodstream might occur or a clot may form causing a pulmonary embolism. The catheter will only be left in the participant's arm for 12 hours, however, so these side effects are not expected. The risks of drawing blood by a single needle poke include: temporary discomfort and pain from the needle stick, bruising, and rarely infection.

Serial blood sampling poses potential risk of anemia or low blood pressure to the participant. All efforts will be made to withdraw the minimal amount of blood during the discard procedure (to remove blood diluted with saline/anticoagulant in the central or peripheral catheter) prior to the actual blood sample draw. Immediately following the blood sample draw an equivolume of saline will be instilled into the participant via the catheter to flush the catheter and to restore volume loss. Participants will also be encouraged to drink plenty of water to help maintain hydration.

The potential risks related to *Cannabis* oil

The efficacy of using cannabidiol in patients to treat seizures associated with Lennox-Gastaut syndrome was recently studied in 171 patients aged 2-55 (Thiele et al, 2018). A safety analysis of the cannabidiol group (n=86) found that the most common events (occurring in more than 10%) were diarrhea (19%), somnolence (15%), pyrexia (13%), decreased appetite (13%), and vomiting (10%). Four patients (5%) in the cannabidiol group experienced an increase in liver transaminases. The dose used in this study was 20mg/kg cannabidiol daily. Similarly, in an open-label trial using CBD to treat seizures associated with CDKL5 deficiency disorder, Aicardi, Dun15q and Doose syndromes (n=55, ages 1-30 years) (50) the most frequently reported adverse effects were diarrhea (29%), somnolence (22%), and fatigue (22%) and decreased appetite (22%). The dose in this study was 2–10 mg/kg/day titrate to intolerance or a maximum dosage of 25 mg/kg/day. Participants in both studies remained on their usual anti-seizure medications throughout the duration of the study (such as clobazam, valproate, lamotrigine, levetiracetam or rufunamide), therefore whether these adverse effects can be directly attributed to the cannabidiol is unclear. The side effect profile is expected to be substantially less in our protocol as the participants will only receive one single dose of cannabidiol oil.

There is also the potential that the cannabidiol will interact with ADHD medications, such as stimulants. In this study we will only be giving the participant one dose of cannabidiol so adverse events are not expected. Nevertheless, determining the safety of a single dose of the herbal extract is an important outcome of our study.

Adverse events
Adverse events of the medications being studied are documented in the CTA product monograph. Any adverse event not listed in the product monograph will be reported appropriately as per Health Canada and local ethics guidelines.

Documentation of patient’s participation
For all patients and caregivers who give informed consent or assent, the investigator will record patient identification data. The patient identification list must allow for the definite identification of any patient that takes part in the study. The investigator will keep the list of patient identification codes for 25 years after completion of the study within the Investigator’s Study File.

Premature discontinuation of the study
If the trial is prematurely terminated or suspended for any reason, trial patients will be informed promptly, appropriate therapy and follow-up for patients will be assured and, where required by the applicable regulatory requirement(s), the regulatory authority (ies) will be informed. The REB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

ANALYTICAL PLAN
LC-MS/MS Analysis
Stock solutions (1 mg mL^{-1} in methanol for cannabinoids and 0.1 µg/mL for internal standards) of cannabinoids and their respective stable isotope labelled internal standards (from Cerilliant Analytical Reference Standards or Cayman Chemical) will be diluted serially with blank human plasma to produce working solutions for the calibration curves. To all plasma samples 610 µL of cold acetonitrile spiked with internal standard (1.6 ng/mL) is added to 200 µL of plasma sample in LoBind microcentrifuge tubes. Following vortex-mixing of 10 seconds and centrifugation of 10 min at 14000 rpm in a microcentrifuge set at 4°C, 700 µL of supernatant is transferred to clean glass tubes and dried in a water bath at 35°C and protected from light for 20 minutes. Samples are

then reconstituted with 200 µL of mobile phase, vortex-mixed for 20 seconds, and transferred to HPLC inserts in amber autosampler vials for LC-MS/MS analysis. Quality control (QC) standards will be prepared similarly as acceptance criteria for each analytical run. The ratio of the peak areas of the cannabinoids to their respective internal standard will be plotted against the nominal concentrations to construct the calibration curve. A linear least-squares regression analysis using $1/X^2$ as weighting factor will be conducted to determine slope, intercept, and coefficient of determination (r^2) to demonstrate linearity of the method.

LC-MS/MS will be carried out using an Agilent 1290 Infinity High Performance Liquid Chromatography system interfaced to an SCIEX QTrap® 6500 mass spectrometer equipped with a Turboionspray™ interface. Applied Biosystems/MDS Sciex Analyst software will be used for system control and quantification. Multiple reaction monitoring will be achieved using electrospray ionization source in the positive ion mode. Analyte separation will be performed using a Zorbax Eclipse XDB-C18 analytical column and mobile phase delivered in isocratic mode (250 µL/min) with 5 µL injection volume.

Sample Size Determination and Power Calculation

Since there is an absence of literature in this area, we are unable to perform a power calculation, and therefore this can be considered as a pilot study. The data obtained from this study will be used to inform future clinical studies.

Statistical Methods

Statistical analyses will be performed using SPSS (version 24) and the PK parameters will be calculated using Graphpad Prism (version 8). The PK parameters will be summarized using descriptive statistics for all participants combined and for participants within each age group. The geometric means and 95% confidence intervals (CIs) will be calculated for Cl_s/F, V_d/F, and AUC_{last} in each age group.

For secondary objective 1 (assessing the safety and tolerability), all adverse effects will be summarized descriptively or listed. For secondary objectives 2-4 (performing comparisons based on age strata, or demographic variables or data obtained from other study populations), relationships between plasma concentrations and age will be determined using analysis of variance (ANOVA) and multiple regression analysis will be used to determine associations between plasma concentrations and demographic variables (age, weight, racial background). Spearman's rho will be used to calculate correlation coefficients. To control for alpha error for these multiple comparisons the level of significance will be set to $P = 0.01$.

Visual inspection of the plasma-concentration time curves will determine the C_{max} and T_{max}. The trapezoidal rule-extrapolation method will be used to calculate the $AUC_{0-\infty}$., while non-compartmental methods will be used to estimate the systemic clearance, mean residence time, apparent volume of distribution (V_d/F), oral clearance (Cl_S/F), half-life, and the log-linear terminal rate constant.

DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Personal information will be treated confidentially. However, this information may need to be reviewed by authorized representatives such as the REB, representatives of the Therapeutic Products Directorate of Health Canada or a designee of the local ethics board. The Investigator acknowledges that the source document and data may be inspected under the authority of the investigator or his qualified designate by representatives of the Sponsor, Health Canada or the Research Ethics Board, as necessary.

QUALITY CONTROL AND QUALITY ASSURANCE

For this research study, the product being utilized will be purchased from CanniMed Therapeutics Inc., a wholly subsidiary of Aurora Cannabis Inc., which is a Saskatchewan based licensed producer of medical *Cannabis*. The product used, regardless of whether it is the matched-ratio or low-ratio, will have only a small amount of the psychoactive ingredient THC, meaning that the extract will contain predominantly CBD as its active ingredient.

The product provided by CanniMed will have its constituents externally verified with regards to concentrations of active ingredients and impurities. The *Cannabis* herbal extract supplied by CanniMed will have traces of medical grade ethanol (a solvent used to extract the CBD and THC) and will be mixed with medical grade olive oil. Using an externally verified compound will allow the researchers to accurately dose the compound for the study participants and minimize the risk of intoxication due to exposure to excessive THC or an impurity.

ETHICS

The study (protocol and consent) will receive ethical approval from the Biomedical Research Boards (REB) and operational approval from the Saskatoon Health Authority (SHA). A Health Canada Clinical Trials Application (CTA) as well as a Health Canada license to obtain the research product. Any modifications made to the protocol after receipt of the REB approval will be submitted as amendments to the REB. Eligible participants will only be included in the study after providing REB approved consent.

The Investigator will ensure that this study is conducted in full compliance with the principles of the Declaration of Helsinki and with the laws and regulations in Canada. This clinical study will be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice.

DATA HANDLING AND RECORD KEEPING

All information collected on the data collection form will be de-identified and no direct personal identifiers will be recorded. All measures will be taken to maintain confidentiality on collected data, however, there is a chance of unintentional release of information connecting the subject with the study.

A list connecting the participant's name to the participant serial number listed on the data collection form will be stored on a password protected computer and access to this list will be limited to study staff.

Data will be stored for 25 years, as per the Health Canada requirements. As per Health Canada requirement, the Sponsor shall maintain all records related to the study for a period of 25 years.

FUNDING AND INSURANCE

Funding Source

Funding has been provided by the University of Saskatchewan College of Pharmacy & Nutrition and College of Medicine.

Insurance

The University of Saskatchewan has General and Professional Liability Insurance to cover legal liability through the Canadian Universities Reciprocal Insurance Exchange (CURIE).

PUBLICATION POLICY

The key design elements of this protocol will be posted on clinicaltrials.gov. Upon study completion, the results of this trial will be submitted for publication and/or posted on clinicaltrials.gov. The results of this study may be presented in a scientific meeting or published, but the identities of the subjects will not be disclosed. The investigators will aim to publish interim results after one year of the study initiation.

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