

Pediatric patients and medical cannabis: new trends

Pacientes pediátricos e cannabis medicinal: novas tendências

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ABSTRACT

BACKGROUND AND OBJECTIVES: Despite the ancestral use of cannabinoids in adults, safety and efficacy in children is unclear. The impact of cannabis on the developing brain is unknown¹. While studies conducted in adults can provide insight into the efficacy/toxicity profile of cannabis, there is a need for specific studies in children and adolescents to understand the impact of cannabis on the developing brain, as well as the potential long-term effects of cannabis use. The objective of this study was to bring a comprehensive view and critical discussion on the subject.

CONTENTS: A narrative review based on research in the PubMed, Medline and Scielo databases was prepared, with an open theme and a selective literature review in the context of the pediatric population.

CONCLUSION: Current research on the impact of medical cannabis use in children and adolescents remains limited⁴, which reinforces the need for robust studies in this population.

Keywords: Cancer, Medical cannabis, Pediatrics.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Apesar do uso ancestral de canabinoides em adultos, a segurança e eficácia na população infantil não é clara. O impacto da cannabis no cérebro em desenvolvimento é desconhecido¹. Embora estudos realizados em adultos possam oferecer informações sobre o perfil de eficácia/toxicidade da cannabis, há necessidade de estudos específicos em crianças e adolescentes para compreender o impacto da cannabis no cérebro em desenvolvimento, bem como os potenciais efeitos a longo prazo do uso de cannabis. O objetivo deste estudo foi trazer uma visão abrangente e discussão crítica sobre o tema.

CONTEÚDO: Foi elaborada uma revisão narrativa baseada em pesquisas nas bases de dados Pubmed, Medline e Scielo, com temática aberta e revisão de literatura seletiva no contexto da população pediátrica.

CONCLUSÃO: A pesquisa atual sobre o impacto do uso da cannabis medicinal em crianças e adolescentes permanece limitada⁴, o que reforça a necessidade de estudos robustos sobre essa população.

Descritores: Câncer, cannabis medicinal, Pediatria.

INTRODUCTION

Historical records report the use of cannabis in the treatment of pain before written history itself, around 3000 BC. Despite ancestral knowledge about the use of cannabinoids and cannabinoid derivatives for symptom control in various situations, scientific evidence around the potential risks and benefits of lifelong cannabis use is unknown¹. The active components of cannabis (CBD, THC, among more than 100 other components) began to be described in the 1960s.

In 1964, the pharmacological properties of cannabis (*Cannabis sativa* L.) made it possible to isolate 9-tetrahydrocannabinol (THC), an important psychoactive component of cannabis. In 1980, the first endogenous cannabinoid, anandamide (AEA), was identified, followed by the discovery of another endogenous cannabinoid compound, known as 2-arachidonylglycerol (2-AG)². In the 1990s, further advances brought the discovery of a cannabis-like system in the human body itself, the endocannabinoid system (ECS), which modulates pain and other physiological systems and conditions in all mammals³.

Cannabinoids are a group of chemicals that bind to receptors in the human body and in turn modulate ECS. Cannabinoids can be endogenously produced, synthesized or derived from the plant *Cannabis sativa* L.

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HIGHLIGHTS

- The impact of cannabis on the developing brain is unknown.
- The role of the endocannabinoid system in mediating neural and cognitive function is not restricted to gestation or early childhood.
- There is a need for robust studies on safety and efficacy in the pediatric population.

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Research in recent decades has shown that ECS is a cellular communication network essential for maintaining multiple biological functions and the body's homeostasis. Cannabinoids influence a variety of biological phenomena, including memory, pain modulation, appetite, movement control, memory creation, reproduction, bone remodeling and immunity, as well as several other physiological processes.

The impact of cannabis on the developing brain is unknown¹. While studies conducted in adults can provide insight into the efficacy/toxicity profile of cannabis, there is a need for specific studies in children and adolescents to understand the impact of cannabis on the developing brain, as well as the potential long-term effects of cannabis use. Current research on these impacts remains limited⁴. For children and adolescents, there is little safety data to guide use in clinical practice^{5,6}.

Cannabinoids act in pain relief through a variety of mechanisms, playing a critical role in peripheral pain, inflammation and hyperalgesia, producing direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, as well as interactions with endogenous and administered opioids, which can potentiate analgesic action^{5,6}.

There is much discussion about the use of cannabinoids as a pharmacological option in a multimodal treatment plan for managing neuropathic pain⁶. With growing knowledge about ECS and preclinical studies indicating that cannabinoid agonists are analgesic, there is increasing attention on their potential role in the treatment of neuropathic pain.

Systematic reviews of randomized trials on the use of cannabinoids for the treatment of adults with chronic non-cancer pain have shown that cannabinoids can be safe and variably effective for neuropathic pain, with no reports of serious adverse effects. Reported adverse effects were generally well tolerated, mild to moderate in severity and led to withdrawal from studies in only a few cases.

Studied cannabinoids included smoked cannabis, oromucosal extracts of cannabis-based pharmaceuticals, nabilone, dronabinol and tetrahydrocannabinol (THC) analog^{7,8}. It has been noted that safety and efficacy have not been established in patients under 18 years of age, mainly due to psychoactive effects.

Another aspect currently under discussion is the use of cannabinoids in childhood cancer. Brain cancers comprise the second most common neoplasm diagnosed in children. Currently, there are no preclinical or clinical studies related to the effects of cannabinoids in pediatric brain cancer, although some evidence shows benefit in relieving symptoms associated with childhood cancer treatment, in particular nausea and vomiting.

To date, most of the understanding on the cannabinoids utility in the management of cancer-associated symptoms or in cancer treatments is derived from studies in adults in which cannabinoid administration was able to increase appetite, reduce chemotherapy-induced nausea and vomiting, and improve mood. However, these studies were limited by small cohorts and heterogeneous cannabinoid products⁷.

Several studies have examined cannabinoids as antiemetic agents in pediatric cancer patients^{1,6,7}, and two randomized, double-blind studies showed that THC was a superior antiemetic com-

pared to placebo⁷. Seizures are a common symptom of brain cancer. Medical cannabis (synthetic or plant-derived extracts) has been investigated in 11 studies for children and adolescents affected by epilepsy. More recently, a single institution in Israel reported its experience over 15 years in 50 pediatric patients (including 9 with brain tumors), in which patients received medical cannabis for cancer and nausea, vomiting, pain, loss of appetite and depressed mood⁷. On the other hand, accumulating evidence associating mental and cognitive health problems with cannabinoid use during adolescence shows the need to investigate its safety and efficacy in pediatric oncology⁷.

In recent years, the medicinal use of cannabis has been approved in different countries for a variety of human conditions. However, the use of these compounds as anticancer agents remains controversial. Studies have shown that cannabinoids have anti-cancer activity in different types of tumors, such as breast cancer, melanoma, lymphoma, and adult brain cancer. Specifically, the phytocannabinoids D9-tetrahydrocannabinol (THC) and cannabidiol (CBD) induced apoptosis and inhibited proliferation of adult cancer cells, as well as modulated angiogenesis and metastasis. Despite growing evidence that cannabinoids elicit anti-tumor effects in adult cancers, little data are available on their effects in children or pediatric cancers⁷.

ECS has wide-ranging effects in mammals and is composed of two G-protein-coupled cannabinoid receptors type 1 and 2 (CB1R and CB2R), their endogenous cannabinoid ligands (endocannabinoids) and the enzymes that regulate their synthesis and degradation. The best-characterized endocannabinoids are 2-arachidonoylglycerol (2-AG) and naraquidonoylethanolamide (AEA or anandamide), which are lipid-based signaling molecules synthesized from arachidonic acid present in the cell membrane. These endocannabinoids mediate different biological functions by binding and stimulating CB1R and CB2R.

Both receptors are expressed throughout the body with abundant expression of CB1R in the central nervous system (CNS) and with CB2R being found primarily on immune cells, with some cell-specific expression in CNS. While many effects of THC are mediated via CB1R and CB2R, CBD has lower affinity for these receptors. In addition, endocannabinoids and phytocannabinoids can bind to and mediate their effects by modulating non-cannabinoid receptors such as adenosine receptors, transient receptor potential cation channel subfamily V member 1 (TRPV1), peroxisome proliferator-activated receptors (PPAR), and other G-protein-coupled receptors, including GPR55 and GPR18. In terms of pediatric cancer, there is a paucity of clinical and preclinical evidence describing the pros and cons of medicinal cannabinoids⁷.

Most research on pediatric cancers has been conducted in leukemia models, especially in T-cell acute lymphoblastic leukemia (T-ALL), a highly aggressive and chemotherapy-resistant cancer, which accounts for 15% of all childhood ALL cases. Several groups have shown that cannabinoids induce leukemic cell death both *in vitro* and *in vivo*. Specifically, these studies have shown that cannabinoids increase intracellular stress and damage mitochondrial membrane potential, resulting in the subsequent release of cytochrome c and the cleavage of caspases 8, 9, 2 and 10.

Importantly, ceramide biosynthesis has been shown to be essential for cannabinoid-mediated activation of the intrinsic apoptotic pathway, as has also been reported in adult glioblastoma models. Furthermore, CBD induces ROS production in leukemia cells, a common mechanism of action found in other cancers, involving an increase in the expression of the NAD(P)H oxidases Nox4 and p22phox.

More recently, a study showed that CBD acts on the mammalian target of rapamycin (mTOR) in leukemia cells, decreasing the phosphorylation of AKT, mTOR and ribosomal S6, affecting the size of leukemia cells⁸. In turn, another study showed that CBD induces cell death by necrosis and autophagy in various types of ALL⁵. Such findings direct an interesting potential for future research in the search for correlations between mTOR pathway, autophagy and apoptosis after cannabinoid treatment in leukemic cells, as occurs in glioblastoma or hepatocellular carcinoma⁷.

Importantly, promising results have also been found when combining cannabinoids with leukemia chemotherapies. Specifically, THC and CBD have synergistic action with doxorubicin, vincristine and cytarabine in leukemia cells *in vitro*. Validating these results *in vivo* would be an essential step towards clinical translation of these data⁷.

Another study, which used a translocation-positive rhabdomyosarcoma xenograft model *in vitro* and *in vivo*, treated with synthetic cannabinoid HU-210 and THC, demonstrated a significant suppression of tumor growth *in vivo*⁷. This finding was consistent with the actions observed for cannabinoid-induced apoptosis in adult cancer cells. This was followed by another group, who investigated the synthetic cannabinoid WIN 55,212-2, a potent CB1R agonist, as an antitumor agent, using a pediatric osteosarcoma model.

In cultured osteosarcoma cell lines, WIN 55,212-2 induced cell cycle arrest and regulated several features of endoplasmic reticulum stress, such as GRP78, CHOP and TRB3, along with subsequent autophagy. These mechanisms of cannabinoid signaling action are consistent with reports from adult cancers⁷.

One study⁵ investigated the effects of THC and CBD on pediatric neuroblastoma, and reported that both THC and CBD significantly reduced the viability of neuroblastoma cells *in vitro*, and CBD prevented xenograft growth *in vivo*. Although the study did not elucidate a mechanism for the antitumor effects of CBD, it was observed that CBD induced apoptosis of neuroblastoma cells both *in vitro* and *in vivo*. Overall, these preclinical data indicate that cannabinoids have potential anticancer efficacy in a variety of different pediatric cancer types, albeit with a variety of reported mechanisms of action. It is important to note that these pediatric cancers have very different cell of origin, exist in different tissue contexts, and are typically driven by tumor-specific mutations. However, across all of these studies and despite the investigation of several different CB1R and/or CB2R agonists, cannabinoids appear to consistently reduce the proliferation of pediatric cancer cells⁷.

However, despite these encouraging data and the known ability of cannabinoids to penetrate the blood-brain barrier, there are no existing preclinical data on the effect of these agents in pediatric

brain tumor models. In line with the paucity of preclinical data on the effect of cannabinoids in different pediatric cancers, to date there are no clinical studies addressing the potential antitumor effect of cannabinoids in childhood cancer. Despite several anecdotal reports describing the anticancer benefits of cannabinoids in pediatric cancer patients, it is not possible to formulate a rigorous conclusion about their true effects. This is because the cannabis products used are varied, ranging from synthetic cannabinoids to whole plant extracts or purified cannabinoids from plant extracts (purified oils).

The exact components of the substances used are not well described, and the concentrations of cannabinoids in plant extracts have not been widely documented (as would be done in a conventional clinical trial). In addition, the cannabinoids' dosage and route of administration differ between reports. Many cancer patients received conventional therapies (such as radiotherapy and chemotherapy) either before cannabinoid therapy or simultaneously. Thus, to date, there are no studies comprehensively showing that cannabinoids have antitumor benefits in childhood brain cancer, but the anecdotal positive responses reported support a significant interest of use in this setting⁷.

Although controlled use of medical cannabis in adults is reported to be safe and well tolerated, it should not be assumed that use is safe for children and adolescents. ECS plays an important role during brain development, with CB1R, 2-AG and AEA being present in the brain from early prenatal development⁷. Endocannabinoids influence neurodevelopment by regulating neuronal migration, while CB1R has been reported to have roles in neuronal precursor proliferation, migration, axonal elongation, synaptogenesis and myelination later in development⁷.

In zebrafish, a common model for ECS research, *in utero* exposure to THC and CBD has been shown to cause morphological defects such as shorter body length, although the concentrations tested were significantly higher than those achievable in human plasma. Studies in murines show that exogenous cannabinoid exposure during embryogenesis can disrupt neurotransmitter systems, resulting in altered motor and reproductive functions, but these studies have only looked at high concentration THC⁷.

The critical role of the ECS in mediating neural and cognitive function is not restricted to gestation or early childhood. During adolescence, CB1R activation mediates the maturation of interactions between prefrontal cortex, amygdala and hippocampus – neural centers responsible for emotion and stress-related behaviors. CB1R-mediated processes are involved in the regulation of neurogenesis, memory, learning, cognition, reward centers, and depression. Therefore, it is conceivable that disruption of normal CB1R functions by exogenous THC use could alter a range of brain functions².

Most reports describing the effects of cannabinoids in adolescents focus on cohorts with self-reported chronic smoked cannabis use, with the amount of THC consumed rarely measured or reported. Inhalation of smoked cannabis can cause short-term physiological effects such as tachycardia, drowsiness and xerostomia, and psychological effects such as paranoia, short-term memory loss and anxiolysis².

Long-term use of cannabis by inhalation in adolescents is associated with mental health problems and drug dependence. However, a rigorous longitudinal twin control study found that short-term cannabis use had no significant effect on IQ or executive functions, even among heavy cannabis users⁵. The study found that family background factors played an important role in predicting that adolescent cannabis users would perform worse on IQ and executive function tests. The notion that lower IQ precedes cannabis use in adolescents is supported by other longitudinal studies⁷.

In a review of five clinical trials looking at CBD treatment in more than 1,000 pediatric patients with Dravet syndrome, a daily dose of 20 mg/kg for up to 14 weeks was found to be safe and well tolerated. Not only did CBD significantly reduce the frequency of seizures in all trials, but the only adverse effects experienced during administration were drowsiness, diarrhea and decreased appetite. Importantly, no adverse mental or cognitive effects were reported. Although these results indicate low toxicity of CBD during the administration period, they are limited due to the lack of long-term cognitive examinations⁷.

Currently, the evidence does not allow to state whether the administration of cannabinoids to children or adolescents may cause long-term disruptions in cognition and neurological functioning or exacerbate central nervous system damage caused by conventional cancer treatments⁴.

Furthermore, current evidence does not allow to state whether cannabinoids can be safely or effectively administered to the pediatric population in combination with other conventional cancer treatments. In the absence of conclusive studies, the American Academy of Pediatrics has adopted a cautious view and does not approve the use of cannabinoids in children⁷. In Brazil, the Federal Council of Medicine (*Conselho Federal de Medicina – CFM*) provides for the use of cannabidiol on treatments of child and adolescent epilepsies that are refractory to conventional therapies in Dravet and Lennox-Gastaut syndrome and tuberous sclerosis complex.

The discussion on the use of cannabinoids in the pediatric population is faced with the need for robust studies on safety and efficacy. As cannabis is increasingly legalized around the world, there is growing and urgent demand for its use by parents of children and adolescents with serious illnesses⁸.

Recent preclinical evidence supports their efficacy and safety in adult brain tumors, with some indications that cannabinoids may interact synergistically with selected chemotherapies – although this has not yet been demonstrated clinically. Despite

promising reports, data showing the potential benefit of cannabinoids for pediatric cancer patients are preliminary.

CONCLUSION

Knowledge about the cellular mechanisms of cannabinoid action in different cancer types or between adult versus pediatric cancers is still not well understood and represents a major challenge when trying to translate results from clinical trials for adults into children.

Unfortunately, existing studies use a wide range of methods to assess the antitumor effects of THC and CBD, different types of cannabinoids (purified from plants or synthetic products), formulations (plant extracts or pure compounds), doses and routes of administration, which may account for differences in observed effects and mechanisms of action.

AUTHORS' CONTRIBUTIONS

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Conceptualization, Data Collection.

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Writing - Review and Editing.

Sandra Caires Serrano

Conceptualization, Data Collection, Writing - Review and Editing, Supervision.

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