A critical narrative review of medical cannabis in pediatrics beyond epilepsy, part I: background

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Background and Objective: In the past few decades, the use of marijuana, now commonly referred to as cannabis in the scientific community, has expanded globally to a myriad of medical conditions beyond epilepsy in pediatrics.

Methods: In this comprehensive review, PubMed, Embase, and Clinicaltrials.gov (1966–May 2020) searches were performed using the key search terms cannabis, medical marijuana, cannabinoids, pediatrics, neurodevelopmental disorders, spasticity, pain, gastrointestinal disorders, and cancer. All article abstracts were evaluated for relevance. Only articles pertaining to cannabis were included.

Key Content and Findings: Cannabis has had an extensive history in medicinal therapeutics, dating back to ancient civilizations. With the recent legalization of cannabis that has augmented its use, a critical review of the medicinal properties and clinical use of cannabis is warranted to support pediatric healthcare practitioners in making informed and evidence-based decisions. In this first section of a three-part series, a comprehensive overview of cannabis and conditions surrounding its use was presented, incorporating its historical perspective, chemical constituents and mechanistic properties within the endocannabinoid system, position for its use by regulatory and professional bodies, ethical considerations, and importance of education of healthcare providers.

Conclusions: Our current understanding of the medical use of cannabis is limited by lack of optimal dosing, long-term efficacy, safety, and drug interaction data in the pediatric population, prompting the need for additional research.

Keywords: Cannabis; medical marijuana; cannabinoids; pediatrics

Introduction

In the past few decades, a rapid rise has been observed in the awareness and acceptance of cannabis for medical and recreational use, partly due to its legalization in many states in the USA. Coupled to this legalization, the broadening scope of research, and changes to the 2018 Farm Bill, which removed hemp [a cannabis plant with less than 0.3% delta-9-tetrahydrocannabinol (THC)] from the Controlled Substances Act, also contributed to the

escalating use of cannabis. Irrespective of the legal status over time, it is clear that millions of people globally use cannabis for a myriad of medical conditions. As research continues to advance, it becomes evident that cannabis has a therapeutic role in many disease states, particularly chronic pain, adjunctive cancer treatment, and epilepsy. However, a growing number of healthcare practitioners, including pediatricians, are recommending cannabis for other medical conditions. Furthermore, adults, young adults and parents of pediatric patients are self-initiating treatment without their practitioner's knowledge.

With the abundant literature evaluating the use of cannabis for epilepsy, this three-part series details the uses beyond epilepsy of cannabis and cannabis-derived products for medical conditions reported in the pediatric population. Currently, evidenced-based data are limited for the medical use of cannabis for conditions beyond epilepsy due to small studies, a lack of standardized cannabis formulations, variability in dosing, and inconsistent methodology. Moreover, much of the available research has been conducted on adults, underscoring the need for pediatricians to extrapolate data and independently evaluate the risks and benefits of use in childhood and adolescence.

This three-part series provides a critical review of the medicinal properties of cannabis to support pediatric healthcare practitioners in making informed and evidence-based decisions for use in their patients. The first section was designed to provide a comprehensive overview of cannabis and its use, incorporating its history, chemical constituents and mechanistic properties within the endocannabinoid system, position for its use by regulatory and professional agencies specifically in pediatrics, the ethical use of cannabis in children, and examination of education furnished to healthcare providers on cannabis therapeutics. The second and third sections focused on the evidence-based treatment of neurodevelopmental disorders, movement disorders, pain associated with movement disorders, epidermolysis bullosa, inflammatory bowel disease, and chemotherapy-induced nausea and vomiting in children and adolescents. Age groups were seldom consistently defined in trials; therefore, in this review, each subgroup within pediatrics was defined and referred to as the following: children (2–12 years), adolescents (13–18 years), late adolescents (19–21 years) and young adults (22–26 years) (1).

We present the following article in accordance with the Narrative Review reporting checklist (available at https://

pm.amegroups.com/article/view/10.21037/pm-20-68/rc).

Methods

This narrative review was conducted by all authors for the purpose of reviewing the available literature on the use of medical cannabis in pediatric disease states. Due to the robust published studies on the use of cannabinoids for epilepsy, the decision was made to narrow our review to other disease states in which cannabis use was not readily known or studied, in order to illuminate providers regarding potential use for other conditions. Our initial search was wide and endeavored to capture any disease state, other than epilepsy, in which any formulation of cannabis was used in the pediatric population. Our search was then narrowed to the following broad medical conditions: autism, behavioral disorders, oncology, autoimmune diseases, spasticity and pain, and genetic and inherited diseases. Based on the limited search results, we organized our findings to report on studies of (1) neurodevelopmental disorders that included autism spectrum disorder (ASD), Tourette syndrome (TS), spasticity, complex motor disorders, and movement disorders, (2) the congenital skin disorder epidermolysis bullosa (EB), and (3) gastrointestinal disorders that included chemotherapy-induced nausea and vomiting (CINV) and inflammatory bowel disease (IBD). Our original intent was to compose one article as a comprehensive review of cannabis use in the disease states outlined above; however, the decision was subsequently made to divide this into a three-part series, allowing a more detailed review of each condition.

Eligibility

The inclusion criteria were only limited to research conducted on the human, pediatric, adolescent and young adult population in the English language. Due to the paucity of search results, there were no limitations on the type of study included.

Information sources

A search in PubMed, Embase, and clinicaltrials.gov up to May 2020 was performed. Our search was conducted using MeSH terms describing cannabis and the particular disease states identified above, for example, "cannabis OR cannabinoid OR medical marijuana AND gastrointestinal disorders" Sources also included websites from relevant

regulatory and professional bodies, such as the American Academy of Pediatrics.

Historical perspective

Marijuana, now commonly referred to in the scientific community as cannabis, has had an extensive history in medical therapeutics (2). Though it has been popularized in the media over the past several decades regarding its recreational and illicit use, *Cannabis sativa L.* has been used by ancient civilizations, such as those in China, India and Egypt, as a healing agent for many ailments including neuralgia, gout, rheumatism, convulsions, delirium tremens, psychosis, and mental depression (3-5). In the 19th century, marijuana was available and dispensed at pharmacies nationwide, and prescribed by physicians for a wide range of ailments. However, in the early part of the 20th century, the USA government imposed the Marijuana Tax Act of 1937, levying heavy taxes on the sale of cannabis, effectively eliminating its use (6). The burden of the tax act was placed on physicians, pharmacists, and farmers and also imposed penalties for noncompliance. Reasons for the passing of the bill were multifactorial and included the League of Nations' ratification of the International Opium Convention designating cannabis as a drug, not a medicine, the USA establishment of narcotic regulations, and general political attitudes associating the dangers of cannabis with the growing immigration population from Mexico and other countries. The bill was opposed by the American Medical Association, led by Dr. William Woodward, who argued that the evidence against marijuana was incomplete and that future investigations into the medical use may show substantial therapeutic effects (7). When this tax act was repealed in 1969, the federal government responded by instituting the Controlled Substances Act which subsequently placed cannabis in the Schedule I category where it remains today, deemed to lack therapeutic effect with high abuse potential (8). This act effectively closed the door to cannabis research. Despite federal law, in 1996, California became the first state to legalize medical cannabis use in adults for serious illness, defined as cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraines, or any other illness for which medical marijuana may provide relief (9,10), paving the way for the many changes to come. Currently, 33 USA states, the District of Columbia, Puerto Rico and Guam have legalized its use for medical purposes and 11 USA states have legalized its recreational use in adults.

While the recent legalization of cannabis has augmented its current medical use, two synthetic cannabinoids, which mimic the effects of THC, were approved by the U.S. Food & Drug Administration (FDA) in 1985: nabilone (Cesamet™ Valeant, Costa Mesa, CA) and dronabinol (Marinol® Solvay Pharmaceuticals, Marietta GA; Syndros™ Insys Therapeutics, Chandler AZ) (11-14), indicated for nausea and vomiting associated with chemotherapy in adults who have failed conventional antiemetics (12). Although both are regulated as controlled substances, nabilone was designated a Schedule II substance, whereas dronabinol was given Schedule III status. Ten years after initial approval, in 1995, dronabinol achieved a second approved indication for anorexia and weight loss in adult HIV/AIDS and cancer patients (13,14). Though these medications have demonstrated success in the pediatric population (11), they are currently administered off-label due to the lack of established safety and efficacy findings. A third cannabis-derived drug, nabiximols (Sativex® GW Pharmaceuticals, UK), is a THC:cannabidiol (CBD) 1:1 oromucosal spray, approved in 25 countries outside of the USA for treatment of muscle stiffness and spasms due to multiple sclerosis in adults. Currently, nabiximols is an investigational product in the USA undergoing evaluations for multiple indications (15).

In June 2018, the FDA approved a non-synthetic, plant-derived CBD oral solution (Epidiolex® Greenwich Biosciences, Carlsbad, CA) for the treatment of Lennox-Gastaut syndrome and Dravet syndrome in pediatric patients above 2 years of age (16,17). Patients with these symptoms experience severe and incessant seizures, have poor motor skills development, and are often refractory to standard anticonvulsants, all resulting in a decreased quality of life. Randomized, double-blind, placebo-controlled clinical trials showed that Epidiolex®, used in conjunction with patients' maintenance anticonvulsant medications, was more effective in reducing the frequency of seizures than placebo (18-20). Interestingly, Epidiolex® is the first FDA-approved drug to contain a purified drug substance from the cannabis plant. Initially designated as a Schedule V substance, Epidiolex® was decontrolled in April 2020 by the Drug Enforcement Administration, eliminating restrictions as a controlled substance, which in turn allowed for increased access to pediatric patients (21).

The endocannabinoid system

Although the cannabis plant has been utilized as a medicine

for millennia, the legal restraints imposed in the early 20th century severely limited research on the pharmacology of the plant. Consequently, the major molecular constituents of the plant, the phytocannabinoids THC and CBD, were not elucidated until the 1960s by Israeli organic chemist, Dr. Raphael Mechoulum (22). Not until two decades later were the endocannabinoids, cannabinoid receptors, and enzymes for synthesis and degradation identified as being a part of the endocannabinoid system (ECS) (23-26). The full magnitude of the ECS is still not completely elucidated; however, it is understood that the ECS is responsible for a broad range of stabilizing and destabilizing activities in the body and may mediate neuroprotection against excitotoxicity, a prominent factor in the pathology of neurodegenerative diseases (27). The modulation of this neurotransmitter system may also result in the therapeutic potential of many other disease states, including inflammatory, metabolic, psychiatric, gastrointestinal, and cardiovascular disorders (28). Since the 1960s, ECS research has exploded and evidence shows that cannabinoid receptors and their ligands are responsible for restoring balance in tissues when injury or disease occurs. Although not fully understood, this complex system may impact other systems in the body, which in turn, modify the ECS (28). Cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2) are G-coupled protein receptors that are distributed widely throughout the body, with CB_1 primarily found in the central nervous system, and CB_2 in peripheral neurons as well as immune cells (27,29). The distribution of the CB receptors accounts for the characteristic effects produced by receptor agonists. The endogenous ligands of these receptors, predominantly anandamide (AEA) and 2-arachidonoylglycerol (2-AG), were discovered by a group led by R. Mechoulam in 1992 (24). Anandamide was named for the Sanskrit word ananda, translating to bliss or happiness, due to the proposed function of the ECS maintaining balance in the body. These retrograde neurotransmitters are synthesized on demand, rather than stored in vesicles, exert activity on receptors residing on presynaptic neurons, and have very short half-lives, degraded by enzymes within minutes. AEA and 2-AG are CB_1 and CB_2 agonists, modifying cell neurotransmitter behavior, resulting in tight control of the balance of GABAergic and glutamatergic transmission via regulation of calcium channels (30,31). Although the therapeutic significance remains unclear, evidence now shows that AEA also activates another cannabinoid receptor, G-protein coupled receptor 55 (32), as well as

non-cannabinoid receptors, such as the transient receptor potential vanilloid channel, an ionotropic receptor (33). The enzyme responsible for the catabolism of anandamide to arachidonic acid has been identified as fatty acid amide hydrolase; 2-AG is metabolized by monoacylglycerol lipase in addition to other catabolic enzymes to a lesser extent (31,34). Due to endocannabinoid lipophilicity, AEA and 2-AG are highly protein-bound in the cell which supports recent evidence demonstrating that fatty acid-binding proteins are responsible for the presynaptic cellular reuptake and delivery of AEA to fatty acid amide hydrolase for metabolism (35).

Phytocannabinoids are lipophilic molecules found in the cannabis plant that have demonstrated similar pharmacologic activity to the endocannabinoids due to their interactions with the CB_1, CB_2, and other cannabinoid and non-cannabinoid receptors. The major phytocannabinoids, THC and CBD, are expressed mainly in the plant as their inactive carboxylic acid forms, THCA and CBDA, and are decarboxylated to active, neutral molecules upon exposure to heat (29). Both major and minor phytocannabinoids are known to interact with receptors within the ECS; however, they differ from endocannabinoids and each other in their distinct receptor affinities, functionalities and physiological effects (36). THC preferentially binds to CB_1, whereas CBD shows little affinity for CB receptors, but instead acts by interfering with AEA reuptake and breakdown, thereby enhancing the activity of AEA. Both THC and CBD also interact with other membrane receptors adding to the complexity of maintaining neurotransmitter homeostasis (37,38). The predominant location of the CB_1 receptor in the brain accounts for the mediation of the intoxicating adverse effects of THC, including euphoria, memory and cognitive deficits, and impaired motor coordination (28). While widely referred to as being 'psychoactive,' both THC and CBD can modulate brain activity; therefore, a more accurate description of the cognitive effects of THC is 'intoxicating' or 'euphoric.' Although THC and CBD are the most well-known and studied of the cannabinoids, research has also focused on the lesser-known minor cannabinoids, such as THCA, CBDA, CBG, CBC and CBN, to elucidate their respective therapeutic value(s) while avoiding the intoxicating adverse effect of THC (39).

THC and CBD are metabolized extensively in the gut wall and liver by the cytochrome P450 system (CYP) to active and inactive metabolites (40). Phase I hydroxylation of THC by CYP 2C9, 2C19 and 3A4 forms the equipotent metabolite, 11-OH-THC. Further oxidation of 11-OH-

THC produces the inactive metabolite, THC-COOH, which further undergoes Phase II glucuronidation for improved water solubility and urinary excretion (40). CBD undergoes hydroxylation by CYP 2C19, 3A4 and 2D6 to form 7-OH-CBD, and is further oxidized to form 7-COOH-CBD. There is no evidence of biologic activity of CBD metabolites (40,41). Like THC-COOH, 7-COOH-CBD is glucuronidated for urinary excretion (40,41).

It is important to note that these phytocannabinoids are substrates for CYP enzymes, and also exhibit enzyme inhibition and induction activities, thereby influencing the metabolism of concomitant drugs. Specifically, it appears that drugs metabolized by the CYP enzymes 2C19, 2C9, 3A4 and 2D6 may be at highest risk for drug-drug interactions (41,42). There are limited studies identifying cannabis drug interactions in humans; however, it is fairly well established that high dose CBD coadministered with clobazam increases concentrations of both clobazam and, to a greater extent, its metabolite N-desmethylclobazam. These results are likely due to the inhibition by CBD of CYP 3A4 and CYP 2C19, respectively (43). Other potentially relevant drug interactions include tacrolimus (44) and warfarin (45,46), although only a few cases have been reported. Healthcare practitioners should be aware of the potential of cannabis products to inhibit the metabolism of other anticonvulsants, such as zonisamide, as well as selective serotonin receptor inhibitors, due to CBD and THC inhibition of CYP 2C19, 3A4, and 2C9. Although the data are limited, concomitant use of CBD and valproate does not appear to affect valproate levels; however, the combination may increase the incidence of liver enzyme elevations (17). Clinical research to illuminate potentially harmful drug interactions is essential.

Recommendations by regulatory and professional bodies

Several regulatory and professional bodies have provided recommendations on the use of exogenous cannabinoids in the pediatric population. The FDA endorses only cannabinoid-derived drugs that have been approved for use under the Federal Food Drug & Cosmetic Act (FD&C Act). As Epidiolex® is the only FDA approved CBD medication, the agency issues concerns for the many unregulated cannabinoid formulations that are being used for self-treatment and cautions consumers regarding the questionable purity and efficacy of these products. Over the past two years, there has been an explosion of CBD products marketed to consumers in retail and online stores, accompanied with overwhelming misinformation and misrepresentation. Alarmingly, a survey of CBD products revealed that only 30% were labeled accurately (47). Because the FDA cannot ensure the safety and efficacy of unregulated products, warning letters have been issued to companies illegally selling and marketing cannabinoid products with unsubstantiated claims (48). However, the FDA clearly acknowledges the significant consumer interest and supports further research into cannabis-derived products and medical therapy (49,50). National professional societies in the USA have issued their positions regarding the use of medical marijuana. Firstly, the American Academy of Pediatrics (AAP) opposes the use of medical marijuana outside of regulations of the FDA (51). However, the AAP endorses compassionate use of medical marijuana for those with a disease that is not unresponsive to usual treatment (52). Furthermore, the AAP acknowledges anecdotal evidence regarding the therapeutic potential of exogenous cannabinoid products and encourages further research (53). Secondly, in 2016, a committee convened by the National Academies of Sciences, Engineering, and Medicine was tasked with performing a comprehensive review of the current evidence of the health effects of using cannabis products. Published in 2017, the final report stated that there is conclusive or substantial evidence to support the efficacy of cannabis and cannabinoids in chronic pain, chemotherapy-induced nausea and vomiting, and multiple sclerosis associated spasticity. The committee also found moderate evidence of efficacy for sleep disturbances associated with certain conditions, and limited evidence for use in appetite improvement, anxiety, post-traumatic stress disorder, and Tourette syndrome. The report also acknowledged that the most robust evidence comes from FDA approved medications and endorses further studies (54). In addition, the Tourette Association of America opposes the use of "medical marijuana" in pediatric patients, including adolescents, due to the lack of robust clinical data and randomized controlled trials. The association does not provide any specific recommendations for FDA approved cannabinoid products (55). Finally, the American Board of Pediatrics and the American Board of Family Medicine do not offer explicit statements regarding exogenous cannabis.

Ethical considerations

Cannabis use in pediatrics, including adolescents, remains

controversial and has not been widely advocated as a valid therapeutic option by many practitioners, in part due to its potential adverse cognitive and intoxicating effects. Several obstacles have hindered the progression of medical cannabis therapy; namely, risk concerns, legal regulations, product standardization, and education of healthcare providers.

A 1995 survey, in which oncologists were asked if they would recommend cannabis more frequently if legal restrictions were lifted and access was increased, illustrated the reluctance of these practitioners to use cannabis regardless of legal status (56). Nonetheless, consumer interest in cannabis has exploded, particularly for cancer therapy as evidenced by the multitude of online resources (57). The dichotomy between the surge of consumer interest and the lack of healthcare provider education is staggering. Neither study of the endocannabinoid system nor cannabis therapeutics is a part of healthcare professional curricula (58,59), signifying that practitioners, including physicians and pharmacists, may inadequately address patients' medical needs. With the abundance of misinformation targeting the public, it is crucial that practitioners obtain the education necessary to competently recommend cannabis for medical use, articulating the benefits and risks to patients and their caregivers (60).

There is some concern amongst practitioners regarding the correlation between the use of cannabis during childhood and young adulthood and the development of psychiatric disorders, primarily schizophrenia, later in life (61). However, studies attempting to link cannabis and schizophrenia are rife with limitations. Most research has relied on observational methods and the heterogeneity of cannabis products and dose is significant. Overall, there is insufficient information and knowledge to associate direct causality between cannabis use in youth and the triggering of psychotic disorders (62). Rather, evidence suggests that the development of schizophrenia and other psychiatric disorders might be attributed to the predisposition to psychosis and heavy cannabis use in youth (63). Nonetheless, with evidence demonstrating the involvement of the ECS in brain development beginning in gestation, risks and benefits of cannabis therapy should be weighed before initiating therapy in the pediatric population (64).

A significant challenge with cannabis therapy for patients and practitioners is the volatile legal environment and inconsistent accessibility that varies by state. Ramifications of federal restrictions include a lack of oversight and standardization of product formulations and testing, as well as limitations to adequate research to elucidate optimal dosing, drug interactions, guidelines and long-term impact.

Conclusion

As the legalization of medical and recreational cannabis continues to expand in the USA and evidence emerges regarding additional therapeutic effects of cannabis beyond epilepsy, the need for further studies becomes imperative. The limitations to our current understanding of the use of cannabis and the lack of data on long-term clinical impact, adverse events (particularly cognitive and intoxicating effects), and drug interactions in pediatrics prompts the need for additional research. In addition, widespread education among healthcare providers, which should encompass optimal dosing, safety and efficacy assessments, legal regulations, and product standardization, is essential to ensure safe and effective use of medical cannabis in the vulnerable pediatric population.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-20-68/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-20-68/coif). JL serves as an unpaid editorial board member of *Pediatric Medicine* from Oct 2019 to Sept 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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