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Clearing the air: Medical marijuana in adolescents with chronic pain

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Introduction

In 2012, the American Academy of Child and Adolescent Psychiatry (AACAP) reported concerns about the negative impact of cannabis in adolescents.[1] In 2019, the AACAP concerns further grew due to legalisation of cannabis and its usage, especially amongst adolescents.[2] One in five Canadian adolescents (aged between 15 to 19 years of age) uses cannabis.[3] There is a global awareness of cannabis usage in adolescents, both medicinally and recreationally. However this research is in its infancy and scanty. This review aims to shed some light on cannabis, its botany, pharmacology and its suitability for adolescents with non-malignant chronic pain.

Cannabis botany

The cannabis plant, also known as marijuana, belongs to the genus Cannabaceae. Cannabis is a genus of flowering plants within the hemp family. A native of Asia, cannabis has been naturalised and cultivated worldwide over thousands of years. Traditionally, three major classes have been recognised: Cannabis sativa, Cannabis indica and Cannabis ruderalis.[4] Cannabis sativa is found worldwide and has very potent psychoactive effects. Cannabis indica is found in India and the Middle East and is also known as Hashish. It has moderate psychoactive properties and Cannabis ruderalis is found in Central Asia and has minimal psychoactive properties. Currently the cannabis plant is being cultivated and engineered as hybrid species where the different species are mixed together to obtain different potencies.

Cannabis plants usually have one of two types of flowers, male or female. Some plants have both. Male flowers grow in elongated clumps along the leaves. They turn yellow and die after blossoming. Female flowers grow in spike-like clusters and remain dark green for a month after blossoming, until the seed ripens. Hashish, more potent than marijuana, is made from the resin of the cannabis flowers.[5]

Marijuana is that part of the plant that consists of dried leaves, flowers, stems and seeds. Medical marijuana or medical cannabis refers to the physician-recommended usage of the cannabis plant and its compounds to treat disease or improve symptoms.[5] Medical cannabis is an all-encompassing term that includes products consumed as smoke, vapours, oils and tablets. Botanical and medical cannabis overlap with no clear cut boundaries for prescription.

Cannabis through time

As of November 2016, marijuana has been legalised in over 40 American states.[6] Some of the earliest records of cannabis usage date back to as early as 3000 BC where traces have been identified in Egyptian mummies. The earliest Chinese records date back to Emperor Shen Nung in 2727 BC In 1000 AD the Arabs used it to treat epilepsy. In 1798 Napoleon took cannabis back to Europe from the Egyptians. In the 1800s cannabis was part of the United States pharmacopoeia where it was a staple in cough syrups and infant diarrhoea medication. In 1941 it was removed from the pharmacopoeia (due to the marijuana tax act) and in the 1960s and 1970s cannabis became highly stigmatised. Currently, research input is being directed to find new uses for an age old drug.[7]

Cannabinoids

The cannabis plant has over 421 chemicals. Sixty-one of these chemicals make up a group of substances known as cannabinoids. A cannabinoid is one of a class of diverse chemical compounds that act on cannabinoid receptors. It is the cannabinoids that give cannabis its properties.[8,9]

Currently two cannabinoid receptors have been identified. These are Cannabinoid 1 (CB1) and Cannabinoid 2 receptors (CB2). CB1 receptors are found in neurons of the brain, spinal cord, peripheral nervous system and in organs and tissues including endocrine glands, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts. They are also highly expressed in the cerebellum, hippocampus and the basal ganglia thus reflecting their importance in motor control, memory processing and pain modulation.The CB2 receptors are mainly found in immune cells, leukocytes, spleen and tonsils. Its functions include modulation of cytokine release in the immune system.[6,8,9]

Activation of CB1 receptors produces marijuana-like effects on psyche and circulation whereas CB2 activation does not. Thus CB2 is being investigated for therapeutic uses like analgesia, chemotherapy and anti-inflammatory effects.

Ligands for the cannabinoid receptor proteins include phytocannabinoids which are cannabinoids found within the cannabis plant, endocannabinoids which are produced within the body and synthetic cannabinoids, which are synthetically manufactured.[9]

Phytocannabinoids are produced by the cannabis plant. Δ-9-tetrahydrocannabinol (THC) is the most psychoactive cannabinoid and most extensively studied. It contributes to the behavioural toxicity and unique pharmacological characteristics of cannabis.[6] Cannabis has been highly stigmatised due to the psychological effects like euphoria, paranoia, distorted perceptions and anxiety.

The mechanism of action of cannabinoids is best demonstrated through THC. THC binds to and is a partial agonist at CB1 and CB2 receptors. When THC binds to CB1 receptors, presynaptic dopamine is released resulting in the psychoactive effects of cannabis.[6] Other phytocannabinoids include cannabinol (which is less powerful than THC), cannibidiol (CBD) and cannabigerol (CBG). These have little or no psychoactive potential and are being isolated from the plant and investigated for potential uses. CBD is being investigated for its analgesic, anti-inflammatory, anti-depressant, anti-epileptic and anti-insomnia effects.[6] The main side-effect is somnolence and due to its lack of neuropsychiatric effects, it looks appealing as a medical drug.

Endocannabinoids refer to a complex, lipid signaling network of neurotransmitters with receptors within the nervous system, organ tissue, connective tissue, glands and immune cells.[6] The two main endocannabinoids are anandamide and 2-arachidonylglycerol (2-AG). Their receptors are CB1 and CB2 receptors. Endocannabinoids play a role in maintaining homeostasis in cognitive processes, fertility, appetite, pain sensation, mood and memory and newer research is focused on its role in psycho-neuro-immunology and mind-body medicine.[6]

Synthetic cannabinoids are available in some countries. Examples include dronabinol, nabilone and nabiximol. Uses include treatment of chemotherapy-induced nausea and vomiting, appetite stimulation in immunocompromised patients, relief of spasticity from multiple sclerosis and childhood epilepsy.[6]

Pharmacology of cannabis and implications in adolescence

Most data on the pharmacology of cannabis is related to THC in adults. Little is known about the pharmacology of THC and other cannabinoids in the paediatric and adolescent population.[7]

In the absence of paediatric and adolescent pharmacokinetic data, adult data becomes a reference point. Adolescents differ not only in body weight but also show changes in body composition, organ size and maturation. This has to be taken into consideration in the pharmacology of cannabis.[7]

Absorption

Administration of cannabis is mainly through smoking, inhalation, vaporisation and ingestion of edible products. Smoked and vaporised cannabis has a rapid absorption with THC detectable in the plasma within seconds and peak concentrations within three to ten minutes.[6] This route provides rapid onset of action and intense effects. Oral ingestion of cannabis allows for a much slower absorption, with peak plasma concentration of THC reached within one to four hours; thus allowing for slower absorption and less intense effects.

Age-related differences in bio-availability and time to maximum concentration will affect absorption in adolescents.[7]

Distribution

THC is highly lipophilic and is initially taken up by highly perfused tissues like the lung, heart, brain and liver and then slowly released from adipose tissue. Age-related differences in the extent of volume of distribution will impact intensity and duration of cannabinoid activity.[7]

Metabolism

Hepatic hydroxylation of Δ-9-THC generates the psychoactive compound 11-hydroxy Δ9 tetra hydrocannibinol (11-OH-THC) and further oxidation leads to the inactive metabolite 11-nor-9-carboxy- Δ 9- tetrahydrocannibinol. Adolescents have similar values to adults for hepatic metabolism. Metabolism occurs via the cytochrome P-450 system. Extra hepatic metabolism occurs in the brain, intestine, tissues and lungs.[6,7,8]

Elimination

Sixty-five percent of THC is excreted in the faeces and 20% in the urine. Anatomical and functional immaturity of the kidney and the discordance in the maturation of glomerular and tubule function can contribute to considerable inter-individual variability in renal elimination in paediatric patients. However, by adolescence the kidney has reached adult maturity.[6,7]

Effects of cannabis on the adolescent brain and behaviour

It has been traditionally known that brain development takes place in utero mainly. Due to the large explosion in neuroscience, it is now evident that brain maturation continues through adolescence and into the mid-twenties.[10] Therefore the adolescent brain is still undergoing development and is considered immature and vulnerable.

The World Health Organization's definition of adolescence is that it begins with the onset of physiologically normal puberty and ends when an adult identity and behaviour appears. This is around the ages of 10 to 19 years of age.[11] During this time of maturation, cognitive functions such as working memory, decision-making and impulsivity control occur.[8]

The adolescent brain is vulnerable and undergoes strong remodelling. Physiological activity at this point includes active development of the endocannabinoid system and changes in cortical volume, grey matter and white matter of the brain.[9] Cannabis usage at this age disrupts brain development by impairing cognitive function and decreasing executive brain function.[10,11] Neuroimaging studies of cannabis users at adolescence has shown a decrease in cortical and subcortical volumes and a decrease in white matter.[12]

Acute cannabis usage in adolescence results in dizziness, deficits in attention, lack of co-ordination, euphoria, abnormal perceptions, anxiety, irritability and paranoia.[12] Chronic usage tends to cause poor school performance with deficits in verbal learning and memory, early school leaving, intellectual disabilities, poor socialisation and even aggressive behaviour. It also has a 1:6 chance of adolescents developing a recognised cannabis use disorder by the age of seventeen. Chronic cannabis usage can even act as a gateway to concurrent substance abuse.[9,10,11]

Medical marijuana and chronic pain

Paediatric and adolescent chronic pain are both under-recognised and under-treated and have an incidence of between 20–35% worldwide.[11,12] The generally accepted definition of chronic pain in adults is pain lasting longer than three months. However in the paediatric and adolescent population it has been redefined to "pain that extends beyond the expected period of healing and therefore lacks the acute physiological signs".[13]

The American Pain Society mentions chronic pain in paediatrics and adolescence as multifactorial. Some of these factors include biological, psychological and socio-cultural factors.[13,14] Chronic non-malignant pain usually presents with abdominal pain, headaches or musculoskeletal pain. The symptoms may vary from anxiety, fatigue, sleep disturbances, depression, learning difficulties, early school leaving and socialisation issues.[14]

When multimodal chronic pain regimens of adjuvant analgesics such as anti-epileptics, anti-depressants and nonsteroidals have proven to be unsuccessful, adolescents turn to cannabis as a possible form of pain relief.

Adolescents who smoke cannabis have a "high" with each use. This "high" is then confused with temporary pain relief.[12]

Currently most of the literature on the use of medical marijuana for chronic non-malignant pain is adult based. There is a paucity of data for the paediatric and adolescent population. A review by Wong et al. looked at one case report of two adolescent patients being treated with dronabinol for pain.[14] They concluded that there was an improvement in pain scores but it was not statistically significant. Harrison et al. examined three case reports on adolescents who use medical marijuana for chronic non-malignant pain and despite smoking medical marijuana, the patients' pain persisted and furthermore these patients experienced difficulties in socialisation and schooling.[12]

The treatment of chronic pain in the adolescent population requires thorough evaluation, adequate management, compliance of adjuvant analgesics and even non-pharmacological management aimed at restorative programmes to improve daily function. It should also involve parents and family members as the entire household's dynamic is affected.[10,11,12] Parenting styles may require modification and schooling options like homeschooling or online schooling may need to be entertained.[10,11,12]

Challenges with medical cannabis

The European Pain Federation has just released literature on how to use medical cannabis in adults.[15] They conclude that therapy with medical-based cannabis should only be considered by experienced clinicians as part of a multidisciplinary team and in conjunction with adjuvant analgesia.[15]All patients must be closely surveyed and if the patient is burdened with any adverse effects, medical marijuana treatment should be terminated.[16] These principles can be extrapolated to the adolescent population until proper adolescent guidelines are formulated.

Despite advances in medical marijuana use in adolescents for epilepsy (Dravet Syndrome), spasticity associated with multiple sclerosis, autism and chemotherapy-induced nausea and vomiting, prescribing medical cannabis has its limitations.[16] These include:

- Delivery method and quality control – The easiest and commonest route of delivery of cannabis remains smoking. It is difficult for practitioners to regulate the actual amount of beneficial cannabinoids being inhaled and the actual amount of THC being ingested contributing to neuropsychiatric symptoms.[16]
- Surveillance for addiction potential – Different individuals have varying adverse effects and addiction potential. Practitioners who start adolescents on medical cannabis need to be trained in constant surveillance for addiction and adverse effects.[16]
- Contaminants – Studies have reported alarming levels of contaminants in cannabis, including bacteria and the fungus Aspergillus. Other contaminants identified include aluminium, cadmium and organophosphates. Glass beads and sand have also been found in street cannabis to increase its value by weight.[16]

Cannabis and the law

South African laws regarding cannabis and its usage are still under scrutiny. As of 18 September 2018, private citizens can no longer be penalised for the possession of cannabis for private use. Based on a person's constitutional right to privacy, Deputy Chief Justice Raymond Zondo of the South African Constitutional Court effectively decriminalised:

a. the use or possession of cannabis by an adult in private for that adult person's personal consumption in private; and
b. the cultivation of cannabis by an adult in a private place for that adult's personal use.[17]

The Constitutional Court ordered the Parliament of South Africa to amend any legislation that did not comply with the above within 24 months.[17]

The South African Health Products Regulatory Authority (SAHPRA) is responsible for regulating all medicines and medical devices in South Africa by ensuring that they meet standards of efficacy, safety and quality. In terms of Sections 21 and 22A(9)(a)(i) of the Medicines and Related Substances Act, authorised practitioners can apply to the SAHPRA for permission to access

and prescribe unregistered medicines when intended to treat individual patients. The Minister of Health has moved CBD from a Schedule 7 drug to a Schedule 4 drug.[18] Furthermore, in light of the uncertainty regarding the way forward on the regulation of cannabis and its usage in South Africa, the Minister of Health has suspended scheduling for a 12-month period for CBD preparations containing a maximum dose of 20 mg of CBD, or raw cannabis products containing not more than 0.001% of THC and 0.0075 mg of CBD. Stakeholders need to consult and decide what to do during this time.[18]

The legislation has not specifically dealt with the paediatric and adolescent population. The government is currently engaging with all stakeholders to develop South Africa's laws regarding cannabis usage, regardless of the motive, and hopefully such engagements don't only deal with usage by adults.[17,18]

In a nutshell:

1. Private usage by adults is allowed.
2. If practitioners want to prescribe cannabis as medicine or to cultivate it, they need to apply to SAHPRA.

As research and data emerge these laws will have to be revisited and the paediatric and adolescent population will have to be considered.

Conclusion

Despite advances in medical cannabis usage and the ability to isolate THC from non-THC or less potent THC compounds, there is still controversy that shrouds the use of medical cannabis for chronic pain in adolescents. The paucity of data available currently does not seem promising but opens up avenues for new research especially with CBD. Legislation also needs to consider the paediatric and adolescent patient population and practitioners need to weigh up the risks versus the benefits when prescribing to an already vulnerable population.

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