

Is the medical use of cannabis a therapeutic option for children?

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Abstract

Cannabis is a psychoactive compound with a long history of recreational and therapeutic use. Current considerations regarding cannabis use for medical purposes in children have been stimulated by recent case reports describing its beneficial effect with refractory epilepsy. Overall, there are insufficient data to support either the efficacy or safety of cannabis use for any indications in children, and an increasing body of data suggests possible harm, most importantly in specific conditions. The potential for cannabis as a therapeutic agent must be evaluated carefully for both efficacy and safety in treating specific paediatric health conditions. Smoking is not an acceptable mode of drug delivery for children. The use of cannabis for medical purposes in specific cases should not be construed as a justification for recreational cannabis use by adolescents. Recommendations for therapeutic use in exceptional paediatric cases are offered, always providing that this treatment course is carefully evaluated in individuals and in ongoing, well-designed research studies to determine safety and efficacy.

Key Words: *Cannabinoids; Children; Epilepsy; Medical marijuana; Nabiximols; Smoking*

Marijuana is a psychoactive substance prepared from the dried flowers and subtending leaves and stems of the female cannabis plant, usually *Cannabis sativa*, which is most commonly consumed by inhalation from smoking.[1] In contrast, cannabis refers to the various psychoactive preparations from the same plant, including marijuana but also hashish (derived from the resin of flowering somites) and cannabis oil. Cannabis has been used as a recreational drug for centuries and it is the most common illicit drug consumed in the world.[2][3]

The medical use of marijuana also goes back centuries. Marijuana was used for therapeutic purposes in China several millennia ago, with its first recorded use in a pharmacopeia appearing in 1500 BC.[4] Marijuana was customarily used to treat insomnia and as an antiemetic before the onset of specific therapies in the 1930s. Subsequently, marijuana has been labelled a drug of abuse in most countries worldwide. In Canada, marijuana was added to the restricted list under the Opium and Narcotic Drug Act by an amendment passed in 1923. Over the past two decades, there has been growing interest in the medical use of cannabis and its preparations in adults, along with increasing discussion around its potential for therapeutic use in children over the past five years.

The psychoactive properties of cannabis are primarily produced by delta-9-tetrahydrocannabinol (delta-9-THC), a cannabinoid that is one of the two major neuroactive compounds found in marijuana.[5] The other major neuroactive compound, cannabidiol (CBD), lacks the psychoactive effects of delta-9-THC but does have behavioural and other central nervous system effects.[1] These compounds bind to G-protein coupled cannabinoid receptors on the membrane of cells in the central nervous system to produce their effects.[5]

New information

Current status in Canada

Using marijuana for therapeutic purposes has included treatment for refractory epilepsy, described in case reports by Gowers and Reynolds from the late 19th century.[5] The development of more potent antiepileptic therapies and the trend toward marijuana prohibition reduced interest in marijuana as a therapy for refractory epilepsy. As time progressed, however, increasing knowledge of brain biology and the potent neuroactive properties of cannabinoids revived interest in its therapeutic potential. In 1996, California became the first American state to legalize the medicinal use of cannabis.[6] Several American states and the District of Columbia have subsequently legalized the use of cannabis for medical purposes, despite the United States Drug

Enforcement Administration's designation of marijuana as a "schedule one" drug, defined under statute as having "no currently accepted medical use and a high potential for abuse". In Canada, medical use of marijuana was sanctioned by Health Canada in 2001, with revisions to the legislation in 2013 (www.gazette.gc.ca/rp-pr/p1/2014/2014-06-14/html/reg1-eng.php). Canadian patients can obtain access to cannabis for medical purposes by visiting a health care practitioner, who can provide documentation to present to a licensed producer, with licensure being regulated on a federal basis. The producer can then supply the patient with up to 30 days' supply, to a maximum weight of 150 g of marijuana. A recent ruling by the Supreme Court of Canada and a subsequent response from Health Canada have effectively removed some restrictions on the form in which cannabis can be supplied to patients. These rulings should permit the therapeutic use of preparations such as specific cannabis oils.

Evidence supporting the therapeutic effect of cannabis in children with epilepsy is sparse. There are animal models demonstrating that delta-9-THC and CBD have anticonvulsant activity in animal models of epilepsy, with the caveat that some studies also demonstrated pro-convulsant activity in healthy animals.[5] In these models, tolerability was limited with respect to delta-9-THC due to psychotropic effects, while CBD was better tolerated. Overall, clinical evidence supporting the use of marijuana and other cannabis derivatives in children is very sparse. Individual case reports have been published; however, evidence tested in randomized or controlled trials is scant.[7][8] One recent Cochrane review identified four studies examining marijuana use for epilepsy.[9] A total of only 47 patients were studied, all of whom were adults. While these studies demonstrated short-term tolerance, no single study reliably demonstrated a reduction in seizure frequency. The authors concluded that the use of marijuana to treat epilepsy needed to be evaluated in properly designed and powered studies.

Much stronger data supports the limited efficacy of marijuana to treat other medical conditions. Studies investigating cannabis use to manage spasticity in adults with multiple sclerosis (MS) have shown that cannabinoids, administered orally, appear to reduce patient-reported spasticity scores, while smoked marijuana was of uncertain efficacy.[10] A similar result was obtained for central pain or painful spasms in adults with MS. There were fewer bladder complaints in adults with MS treated with nabiximols, one of three medications derived from cannabis and approved for use in Canada, although no effect was demonstrated using other oral cannabinoids. Cannabinoids also appeared to be ineffective for controlling tremors in adults with MS, chorea in adults with Huntington's disease, levodopa-associated dyskinesia in adults with Parkinson's disease or tics in adults with Tourette's syndrome.[10]

Cannabis continues to be considered as a potential therapy in conditions for which there are, essentially, no data supporting its use. There have been no studies demonstrating the efficacy and safety of marijuana use to control children's pain or nausea.[11]

Potent medications can be accompanied by significant, potentially adverse side effects. It is well recognized, for example, that many drugs commonly used for seizure therapy in children are also associated with negative effects on behaviour and learning. The most predictable side effects associated with marijuana use are red eyes, dry mouth, delayed motor skills and tachycardia;[12] however, reviews of the medical use of cannabis have also identified adverse events. A review of studies investigating marijuana use for selected neurological disorders demonstrated that 6.9% of 1619 patients treated with a cannabinoid for <6 months stopped use due to adverse events, compared with 2.2% of 1118 subjects in the control group.[10] While these effects were not well characterized, they included nausea, weakness, mood changes and anxiety. Studies focused on cognitive impairment appeared to show twice the degree of cognitive impairment among patients treated with marijuana compared with controls.[10][13] Cannabinoid use in one randomized clinical trial involving patients with MS was associated with a higher suicide risk compared with placebo controls.[14] All of these studies involved adult patients. There is ongoing controversy regarding cannabis use being associated with a risk for serious mental health disorders such as psychosis. The data linking marijuana use with a higher risk for psychosis were highlighted in a recent study which demonstrated that up to one-quarter of cases of new-onset psychosis were associated with the recreational use of high-potency cannabis.[15][16]

There is a small body of literature suggesting that the magnitude of cognitive effects of cannabis may be age dependent. One small study focused on adolescents with attention deficit hyperactivity disorder who used marijuana regularly, and found an association with impaired executive function and, potentially, for impaired cognitive function when marijuana use was initiated before 16 years of age. When regular marijuana use was not started until after 16 years of age, there was no apparent aggravation of cognitive deficits associated with attention deficit hyperactivity disorder.[17] One neuroimaging study examining young adult recreational marijuana users showed differences in grey matter density, volume and shape compared with controls.[18] Chronic marijuana exposure is associated with adverse effects on the functional integrated relationship among spatially separated brain regions that may be exaggerated when exposure begins during adolescence.[12][19]-[21] While there are no data regarding the impact of cannabis use on the brains of younger children, it is probable that effects would be similar. Even these limited findings have implications for the medical use of cannabis in children.

In the context of recreational use, there are usually periods when the concentration of cannabinoids in the blood is low or minimal. In contrast, in a therapeutic context, such as using cannabis to manage intractable epilepsy, one goal would be to maintain a relatively constant concentration of cannabinoids in the bloodstream over time. Therefore, future research investigating cannabis use for medical purposes in children must include longitudinal developmental assessments, ideally with neuroimaging, and discussions about informed consent to participate in these studies need to include such considerations of effect. In conditions for which cannabis is used as a therapy of last resort, there should be a robust and complete discussion with the patient (when possible) and the family regarding the potential risks and benefits. The therapeutic course must be monitored closely for evidence of both efficacy and toxicity.

In common with many other potent psychotropic agents, marijuana use is associated with risk for dependence.[22] Risk levels range between 9% and 50% among recreational marijuana users and appear to be higher when marijuana use begins in adolescence and occurs on a daily basis.[21] Discontinuation of cannabis among chronic users is commonly associated with withdrawal symptoms including headaches, sleep disruption, irritability and anxiety.[23]

One issue germane to marijuana use for treating children is that it is usually smoked. There are several compelling reasons why smoking is an unacceptable drug delivery system for younger populations. Combustion produces tars and other by-products known to be associated with long-term harmful effects, most notably carcinogenesis. The delivery of drugs by smoking also makes it difficult to control or adjust dosage. This difficulty is especially relevant in that the THC content of marijuana available today is two to four times higher than from typical plants used decades ago.[21][24] There is also considerable variability in THC content batch-to-batch.[21] Should cannabis be demonstrated to be an effective and safe therapy for selected health conditions in children, a more appropriate and stable dosing form other than smoking should be used. Recent rulings governing the availability of cannabis for medical purposes in Canada could open the way for other formulations.

As with other psychoactive agents, being able to demonstrate the efficacy and safety of cannabis use for medical purposes in thoughtfully designed, carefully monitored therapies for selected conditions in children is neither a rationale for, nor supportive of, the recreational use of marijuana by children or adolescents. One recent study from the United States that compared marijuana use in adolescents in states where cannabis for medical purposes was available with states where it was not, found there was no increase in recreational use where it was legal.[25] In contrast, a study in Colorado – where cannabis use for medical purposes is available – tracked attitudes toward and trends in marijuana use among adolescents, and demonstrated both lower risk-perception and a higher rate of marijuana use among 12- to 17-year-olds, compared with states where it was not available.[26] The same research group described a significant increase in motor vehicle fatalities where marijuana use was a factor following the legalization of marijuana for medical purposes in Colorado.[27]

If and when cannabis is proven to be therapeutically efficacious and safe, it must be regulated with the same care and precision as other psychoactive therapeutic agents.[28][29] The “medical marijuana” industry must also be subject to the same regulatory standards, legislative controls and degree of oversight as the pharmaceutical industry. Consideration of the particular safety issues germane to children must remain front and centre in the decision to treat exceptional paediatric cases.[30]

Recommendations

- While anecdotal evidence and biological plausibility suggest that cannabis and its derivatives may be an effective treatment for refractory epilepsy in children, its efficacy in this population should be carefully evaluated over the long-term, using appropriately supported and well-designed research into developmental effects, including neuroimaging (level of evidence: 4).[31]
- Medical evidence and biological plausibility suggest that therapeutic use of cannabis may have significant adverse effects in children. Risks should be carefully evaluated over the long-term, using appropriately supported and well-designed research into the safety issues specific to children, including development and neuroimaging studies (level of evidence: 3).
- Smoking as the customary mode of delivery for marijuana is unacceptable in children for several reasons. Studies investigating cannabis use for medical purposes in children should explore alternative delivery systems to provide safe and consistent drug concentrations (level of evidence: 3).
- While research is ongoing, the use of cannabis for medical purposes in children should be evaluated on a case-by-case basis, and always with a comprehensive discussion of potential benefits and risks. Treatment plans that include cannabis should be constructed with careful attention to dose-finding, evaluation of efficacy and safety monitoring, and should only be conducted by clinicians or health teams with condition-specific expertise and the ability to assess for, and evaluate, both efficacy and toxicity (level of evidence: 4).
- Using cannabis to treat neurological conditions in children should be evaluated in accordance with a careful research strategy. The decision to study cannabis use for a specific condition should always be based on the biological plausibility of efficacy and on evidence determined by well-designed clinical trials (level of evidence: 4).
- Clinicians who treat children with cannabis should have specific expertise and training in the use of potent psychoactive drugs in this population. Treatment should be predicated by robust discussions with the patient (if possible) and family concerning the goals and potential risks of this choice, with a strong monitoring strategy in place to test for efficacy and adverse effects.
- There is biological plausibility that cannabis may produce harm if used to treat certain conditions in children, especially when started at an early age (level of evidence: 4).
- The selective use of cannabis for medical purposes in children must not be confused with condoning its recreational use by adolescents. Strategies to discourage its recreational use among adolescents should be developed on models underway to discourage alcohol and tobacco use in this age group (level of evidence: 3).

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