Serious adverse events related to cannabis used for medical purposes

CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

PROTOCOLS

Principal investigators

Lauren E. Kelly, PhD, Department of Pediatrics and Child Health, Department of Community Health Sciences, George and Fay Yee Centre for Healthcare Innovation, University of Manitoba, 405-753 McDermot Ave., Winnipeg MB R3E 0T6; lauren.kelly@umanitoba.ca

Geert ‘t Jong, MD, PhD, Department of Pediatrics and Child Health, Children’s Hospital Research Institute of Manitoba – Clinical Research Unit, 539E-715 McDermot Ave., Winnipeg MB R3E 3P4; geert.tjong@umanitoba.ca

Co-investigators

Richard E. Bélanger, MD, Department of Paediatrics, Centre mère-enfant Soleil - CHU de Québec - Université Laval

Yaron Finkelstein, MD, FACMT, Department of Paediatrics, University of Toronto, The Hospital for Sick Children

Christina Grant, MD, Division of Adolescent Medicine, Department of Paediatrics, McMaster University

Charlotte Moore-Hepburn, MD, Division of Paediatric Medicine, The Hospital for Sick Children

Rod Rassekh, MD, Division of Oncology, Department of Pediatrics, University of British Columbia

Lawrence Richer, MD, Division of Neurology, Department of Pediatrics, University of Alberta

Michael Rieder, MD, PhD, Department of Pediatrics, Western University

Hal Siden MD, Medical Director, Canuck Place, Department of Pediatrics, Inter-Departmental Division of Palliative Medicine, University of British Columbia

Collaborators

Hanan Abramovici, Health Canada
Stephanie Jack, Health Canada
Julie Laroche, Health Canada
Shehnaaz Merali, Health Canada

Background

Cannabinoids are used for medical purposes in children and adolescents for a variety of labelled and off-label conditions including seizures, pain, migraine, nausea, autism, and cancer.[1-3] Cannabinoids are naturally occurring chemical

compounds of the *Cannabis* plant (*Cannabis sativa* and *Cannabis indica*) found in various proportions and concentrations dependent on species, breeding, and growing conditions.[4] Cannabinoids act on endocannabinoid receptors throughout the body, primarily cannabinoid receptor 1 in the central nervous system and cannabinoid receptor 2 located on immune cells.[5] The two most prevalent cannabinoids are Δ9-tetrahydrocannabinol (THC, psychoactive and hallucinogenic properties) and cannabidiol (CBD, no hallucinogenic properties).

Cannabinoids have been used to manage nausea and vomiting in children with cancer.[6,7] Compared with prochlorperazine, children receiving nabilone, a pharmacological cannabinoid derivative, have reported better control of retching, nausea, and vomiting but were more likely to experience adverse events.[6] In two recent publications by Devinsky et al.[8,9], the use of a cannabidiol oral solution for treating drug-resistant seizures was linked to a higher frequency of adverse events than placebo, with 10/60 children reporting serious adverse events (SAEs) and roughly one third of the children randomized to receive cannabidiol presenting with either diarrhea (31%), decreased appetite (28%), or somnolence (36%).[8,9] About 5% of children in these two randomized control trials discontinued the cannabinoid product because of SAEs. However, another small open-label dose-finding and tolerability study reported no (0/19) participant withdrawals or SAEs, despite the addition of a high concentration of cannabidiol product to regimens of multiple antiepileptic drugs.[10]

The ease of accessibility to cannabis and cannabis legalization in Canada have increased public interest in cannabis use for medical purposes. The impact of the October 2018 legalization of recreational cannabis use for adults in Canada is unknown related to the demand, use, and adverse effects of cannabis for medical purposes in the paediatric population. Similarly, the impact of the promotion of cannabis use through online parent communities such as Mothers Advocating Medical Marijuana in Autism (MAMMA) is unknown. In September 2018, the Collège des médecins du Québec removed the requirement for patients taking cannabis authorized in Quebec to be enrolled in a research project, removing a valuable mechanism to collect safety data.[11]

Health Canada has not approved any product containing cannabinoids for use by children or youth and recreational cannabis use is prohibited for those younger than 19 years of age. There is little real-world data on adverse events in Canadian children using cannabis products for medical/therapeutic purposes and limited knowledge about what products and what adverse events are common in children. Formal evaluation of the use of health products containing cannabis and cannabinoids is critical due to limited evidence for effectiveness, potentially life-threatening adverse events, and a high rate of reported adverse events and short-term toxicities (including coma and severe hypotension). There is also the potential for long-term disruption of the endocannabinoid system which may impair neurodevelopment.[12-14]

A previous survey by the Canadian Paediatric Surveillance Program (CPSP) reported that 50% (419/835) of responding paediatricians had encountered paediatric patients using cannabis for medical purposes, and more than one third

(316/835) had been asked by a parent or adolescent for a medical cannabis authorization.[15] Most responding Canadian paediatricians (90%; 752/832) were unaware of how to authorize cannabinoids for medical purposes in persons under 18 years of age, or how to monitor for efficacy and side effects.[10] There is limited scientific evidence on the incidence, management, and outcomes following adverse events in children and youth exposed to medical cannabis, creating a knowledge gap for physicians and nurses managing these patients.

Methods

Using the established CPSP methodology,[16] over 2,800 paediatricians and paediatric subspecialists will be surveyed monthly over a two-year study period and asked to report all new cases of SAEs related to cannabis used for medical purposes in Canadian children and youth. CPSP participants who identify a case on the monthly reporting form will be asked to complete a detailed questionnaire seeking non-nominal demographic and clinical information.

Case definition

Report any serious or life-threatening adverse event* in a child up to 18 years of age related to the intentional use of cannabis for medical purposes.† Report an adverse event even if there is no certainty it is related to the use of cannabis.

Include any cannabis product from a licensed producer or private producer (home grown) such as dried cannabis to be smoked or vaporized, oils to be ingested or applied topically, and cannabis products taken by any other route of administration.

* A serious or life-threatening adverse event is defined as a noxious and unintended severe response to a drug which occurs at any dose and results in emergency observation, hospitalization, persistent or significant disability, or death.

† Cannabinoids or cannabis used for medical purposes is defined as intentional cannabis use for any self-reported (or parent reported) health reasons, with or without physician authorization.

Exclusion criteria

- Adverse events resulting from recreational cannabinoid/cannabis use
- Adverse events resulting from accidental/unintentional cannabinoid/cannabis exposure (even if being used medicinally by another individual in the home)

Objectives

1) Describe the clinical characteristics, including indication, exposure, and concomitant medications, of Canadian children and youth following SAEs related to the authorized or unauthorized use of cannabinoids or cannabis for medical purposes
2) Describe the management and outcomes of patients following SAEs related to the authorized or unauthorized use of cannabinoids or cannabis for medical purposes

Duration

December 2019 to November 2022

Expected number of cases

In children, cannabinoids are used to manage a variety of health issues. The expected number of adverse events associated with cannabinoids in children is challenging to predict as no formal surveillance program exists and parents accessing unregulated products may be hesitant to self-report.

In the 2017 CPSP survey on cannabis for medical purposes among Canadian children and youth,[15] 50% (419/835) of responding paediatricians had encountered children using cannabinoids for medical purposes (either authorized or unauthorized) in the past 12 months. The CPSP network of 2,800 paediatricians has an average response rate of 82% to the monthly reporting forms,[16] with an estimated 2,000 report forms submitted each month. In accordance with previous studies showing that SAEs occur in 12% to 17%[9] of children receiving cannabinoids, and 50% of CPSP pediatricians reporting at least one patient with a medical cannabis exposure, it is anticipated that the CPSP will receive approximately 150 reports of medical cannabis-related SAE cases per year.

Study limitations

All adverse events related to cannabis are considered suspicions as a definite causal association often cannot be determined. Some patients and caregivers may choose not to disclose the use of medical cannabis to their health care provider and therefore these cases would be missed. It may be challenging to estimate the dose and the amount of cannabinoids in cannabis products (dried leaf) used to manage health concerns in self-medicating youth. As with any voluntary reporting surveillance system, there may be under-representation of the disease/condition in the population. It is possible that some groups of children may be missed, for example, those living in rural or remote areas who may be less likely to receive timely paediatric specialist care, and youth approaching transition to adult care (16 to 18 years) who may be more likely to present to an adult provider/facility.

Despite the stated limitations, surveillance provides important clinical data on SAEs resulting from cannabinoid or cannabis exposure for medical purposes in Canadian children and youth.

Ethical approval

- Health Canada and the Public Health Agency of Canada's Research Ethics Board
- University of Manitoba Health Research Ethics Board

Analysis and publication

Data will be used to describe the characteristics, management, and outcomes of SAEs related to cannabinoids and cannabis used in children for medical purposes. The information will be used to inform policies on cannabinoids used for medical purposes in children and raise awareness of possible risks while providing Health Canada with valuable data on the frequency and management of SAEs. The investigators will engage with the Canadian Paediatric Society to update position statements and practice points on medical cannabis use in children that can be

shared with paediatric care providers, as well as provincial and federal authorities. Establishing potential products and dosing at which SAEs are occurring with authorized or unauthorized cannabinoid use may help to inform the maximum doses in clinical trials and future clinical practice guidelines.

The study results will be submitted for publication in an open-access, peer-reviewed journal to ensure parents and practitioners can easily access our findings. Summary data will be shared through the multi-disciplinary Canadian Childhood Cannabinoid Clinical Trials Network and the Maternal Infant Child Youth Research Network. The results will also be shared at national and international conferences, directly with representatives at Health Canada, and with researchers seeking to evaluate health products containing cannabinoids for children.

References

1. Wong SS, Wilens TE. Medical cannabinoids in children and adolescents: a systematic review. *Pediatrics* 2017;140(5):e20171818.
2. Poleg S, Golubchik P, Offen D, Weizman A. Cannabidiol as a suggested candidate for treatment of autism spectrum disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2019 Mar 8;89:90–6. doi: 10.1016/j.pnpbp.2018.08.030. Epub 2018 Aug 29.
3. Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. *Chem Biodivers* 2007;4:1614–48.
4. Sawler J, Stout JM, Gardner KM, et al. The genetic structure of marijuana and hemp. *PloS ONE* 2015;10:e0133292.
5. Pertwee RG. Cannabidiol as a potential medicine. In: Mechoulam R. (eds) *Cannabinoids as Therapeutics. Milestones in Drug Therapy MDT*. Birkhäuser Basel 2005:47–65.
6. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics* 1987;79:946–52.
7. Dalzell A, Bartlett H, Lilleyman J. Nabilone: an alternative antiemetic for cancer chemotherapy. *Arch dis child* 1986;61:502–5.
8. Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. *N Engl J Med* 2018;378:1888–97.
9. Devinsky O, Cross JH, Wright S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med* 2017;377:699–700.
10. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. *Ann Clin Transl Neurol* 2018 Aug 1;5(9):1077–88.
11. Ordonnance de cannabis à des fins médicales: Mise à jour 09/2018 Directives. Collège des médecins du Québec 2018. (Accessed 22 October, 2018, at http://www.cmq.org/publications-pdf/p-1-2018-09-20-fr-ordonnance-cannabis-fins-medicales.pdf.)

12. Schonhofen P, Bristot IJ, Crippa JA, et al. Cannabinoid-Based Therapies and Brain Development: Potential Harmful Effect of Early Modulation of the Endocannabinoid System. *CNS Drugs* 2018 Aug;32(8):697–712.
13. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Eng J Med* 2014;370:2219–27.
14. Campbell CT, Phillips MS, Manasco K. Cannabinoids in pediatrics. *J Pediatr Pharmacol Ther* 2017 May-Jun;22(3):176–85.
15. Belanger R GC, Breakey V, Donner E, Laflamme J, Pinard AM, Rieder M Cannabis for medical purposes among Canadian children and youth. *CPSP 2017 Results*. Canadian Paediatric Surveillance Program, Canadian Paediatric Society 2018:37–8.
16. Grenier D, Doherty J, MacDonald D, et al. Canadian Paediatric Surveillance Program evaluation: an excellent report card. *Paedtr Child Health* 2004; 9:379–84.
17. Pinhas L, Morris A, Crosby RD, Katzman DK. Incidence and age-specific presentation of restrictive eating disorders in children: a Canadian Paediatric Surveillance Program study. *Arch Pediatr Adolesc Med* 2011 Oct;165(10): 895–9.