Symptoms, adverse events, and outcomes in the use of medicinal cannabis in children and adolescents with autism spectrum disorder: a scoping review protocol

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ABSTRACT

Objective: The objective of this scoping review is to map and identify the symptoms, adverse events, and outcomes in the use of medicinal cannabis in children and adolescents with autism spectrum disorder.

Introduction: Autism spectrum disorder is a neurodevelopmental disorder that impacts social communication and social interaction, and is associated with restrictive and repetitive behaviors and interests. Medicinal cannabis has become a potential area of interest for parents for the treatment of autism spectrum disorder symptoms in their children. There is some evidence that cannabinoids may be involved in autism spectrum disorder, laying a potential foundation for medicinal cannabis utility; however, previous reviews did not identify any clinical research on this topic.

Inclusion criteria: This scoping review will consider all published and unpublished studies that investigate the use of medicinal cannabis in autism spectrum disorder, where at least 50% of the participants have a diagnosis of autism spectrum disorder and at least 50% of the study population is 0 to 18 years of age, or where pediatric data are reported separately. Studies undertaken in any context (hospital or community) and in any geographic location will be included.

Methods: We will search MEDLINE, Embase, CINAHL, PsycINFO, Web of Science, and Google Scholar, and the gray literature sources for studies. Two independent team members will screen titles and abstracts, review full texts for potential inclusion, and extract data for all studies. The results will be presented as a narrative synthesis and in tabular form.

Keywords: autism; autism spectrum disorder; medicinal cannabis; pediatrics


Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that has become increasingly prevalent in recent years. In Canada, the most recent statistics indicate that one in 66 children and youth aged five to 17 years have been diagnosed with ASD.¹ Autism spectrum disorder is characterized by deficits in social communication and social interaction, as well as restricted, repetitive patterns of behavior, interests, and activities.² As a spectrum disorder, there is wide variability in the manifestation and functional impact among patients.³ To date, there is no cure for ASD, and existing interventions and treatments aim to facilitate learning and skill acquisition, and improve functional skills (eg, communication or self-care) and quality of life (eg, recreation and leisure, health and well-being).⁴ Behavioral intervention, in particular applied behavioral analysis, is currently the standard of care for individuals with ASD.⁴ These interventions primarily target skill acquisition in areas of deficit. There is evidence for the efficacy of applied behavioral analysis in young children with ASD, with effective sizes ranging from 0.3 to 1.0⁵; however, it is not effective for all children with ASD and there is little evidence available for older children.⁴,⁵ Currently, there are no pharmacological treatments that target the core symptoms of ASD, although some
Atypical antipsychotics, for example, have some evidence for reducing irritability, aggression, and repetitive behaviors; attention-deficit/hyperactivity disorder (ADHD) medications (for ADHD-like behaviors or a comorbid ADHD diagnosis) have been shown to moderately improve hyperactivity symptoms; and melatonin (for insomnia) has improved sleep time by approximately one hour per night. Interventions, such as applied behavioral analysis, have a specific time frame when they can be effectively implemented, and other pharmaceutical interventions, such as atypical antipsychotics, have side effects (e.g., weight gain). As a result, parents of children and adolescents with ASD may turn to unproven therapies, in part due to the lack of efficacious medical treatment, side effects from pharmaceutical interventions, and limited therapeutic options for ASD. A systematic review found that across studies, 28% to 95% of parents of children and adolescents with ASD used complementary and alternative medicines. Forty-five percent of these studies included populations from the United States, and the remaining studies were from Australia, Canada, China, New Zealand, and several European countries. This suggests that parents are not satisfied with standard treatments for the behavioral manifestations of ASD. Within this climate, medicinal cannabis has become a potential area of interest for parents for the treatment of ASD in their children, as use of cannabis has been reported in other childhood conditions.

The recent expansion of medicinal cannabis research parallels increasing legalization of both medicinal and recreational cannabis in countries where cannabis has been legalized. In Canada, medicinal cannabis was made legally available in 2001, and recreational cannabis was nationally legalized in 2018. At the same time, reports of potential efficacy of medicinal cannabis to treat ASD symptoms in children have appeared in mainstream media. A 2015 systematic review and meta-analysis found moderate-quality evidence for medicinal cannabis for only two conditions: chronic neuropathic or cancer pain (odds ratio of 1.41 for substantial pain reduction relative to placebo; −0.5 points on a 10-point pain scale) and spasticity due to multiple sclerosis or spinal cord injury (greater average improvement on spasticity scales vs. placebo). The same systematic review also found low-quality evidence for Tourette syndrome, chemotherapy-induced nausea and vomiting, weight gain in patients with HIV, and sleep disorders. However, given the rapidly evolving nature of this field, more research on the use of medicinal cannabis for other conditions is likely to have been published since this review was completed. In the pediatric population specifically, evidence from a 2019 systematic review found four high-quality randomized controlled trials (along with 19 other clinical studies) showing that cannabidiol products are beneficial in reducing seizure frequency in children with refractory epilepsy by an average of 20%.

Cannabinoids, including tetrahydrocannabinol (THC) and cannabidiol (CBD), act on the body’s endogenous endocannabinoid system. Animal models of ASD have found alterations in the endocannabinoid signaling system and that enhancement of endocannabinoid signaling corrects social impairment. Further, clinical studies show changes in the endocannabinoid system in ASD. One study found changes in cannabinoi receptor expression in peripheral blood cells of children with ASD and another study found that endogenous endocannabinoid serum levels are altered in children with ASD. This body of work provides a biological and chemical background suggesting that medicinal cannabis may have an effect on ASD symptoms. Previous reviews have examined the evidence for medicinal cannabis in treating medical conditions in pediatric populations. A systematic review conducted in 2017 looked broadly at the use of medicinal cannabis for pediatric medical conditions, but found no studies examining ASD. The lack of research regarding medicinal cannabis in ASD at the time of that review highlights a significant knowledge gap. However, medicinal cannabis research is a rapidly evolving field, and a preliminary literature search reveals that since the completion of the above-mentioned reviews, there have been a number of published clinical studies investigating the use of medicinal cannabis for behavioral symptoms of children with ASD.

Despite the promising evidence, there remain significant concerns about the safety of medicinal cannabis, especially for children who have a developing brain that may be vulnerable to the effects of cannabis. Previous studies on the recreational use of cannabis in youth have highlighted potential side
effects such as impacts on the activation patterns of frontal cortex areas associated memory and executive function, and increased risk of psychosis, with an odds ratio of 1.41. Current policy reflects this substantial concern of harm. In 2016, the Canadian Pediatric Society published a position statement on medicinal cannabis in children, stating that there is only sufficient evidence to recommend usage in persons with epilepsy, and on a case-by-case basis in exceptional circumstances for other conditions.

The American Academy of Pediatrics’ position statement on marijuana, released in 2015, states that the organization does not support the use of medicinal cannabis due to insufficient efficacy evidence and a high risk of harm to children and youth. For medicinal cannabis to be recommended for the treatment of ASD, substantial research evidence supporting its use is necessary to would allow these societies to change their position statements.

There is a clear need for synthesis of emerging information regarding the use of medicinal cannabis in the treatment of ASD. Such evidence is especially necessary in the pediatric population where impacts of brain development are of key concern. A scoping review is an efficient way to address this current knowledge gap, by summarizing information currently available in the literature, hopefully assisting clinicians in providing children and families with advice, and highlighting areas where future research is still needed. This scoping review is intended to be a preliminary synthesis of the literature that will identify and map which symptoms medicinal cannabis may be used to treat, potential safety concerns, and outcome measures. This mapping of the literature could be used to determine which symptoms and outcomes should be considered in a future systematic review and meta-analysis.

A preliminary search of MEDLINE, PROSPERO, and Google Scholar was conducted on October 7, 2019, to search for existing systematic or scoping reviews on this topic. We identified one in-progress systematic review in PROSPERO on cannabidiol for ASD, but it is not pediatric-focused. Additionally, this systematic review has more limited search methods and may be at risk of publication bias, as it includes only peer-reviewed studies found in commercial databases and theses. Publication bias may occur because statistically significant or positive results are more likely to be published in journals than studies with negative or non-significant results.

In contrast, we will perform a comprehensive search of the gray literature, and we will include studies published in all formats, including conference proceedings. These search methods and inclusion criteria may lead to more studies being identified and included in our review, providing a more complete map of the evidence.

**Review question**

What is the scope of currently available evidence on the use of medicinal cannabis in children with ASD with regard to symptoms treated, adverse events, and outcomes?

**Inclusion criteria**

**Participants**

This scoping review will consider studies where at least 50% of the participants have a diagnosis of ASD and at least 50% of the study population is 0 to 18 years of age, or where pediatric data are reported separately. A cut-off of 50% for these criteria will allow us to include studies with a majority of pediatric patients and a majority of participants with ASD diagnoses in the context of studies that may have included multiple diagnoses or a wider age range. When ASD or pediatric data are reported separately, we will exclude the other conditions or adults from our analysis.

**Concept**

For the purpose of this review, the term “medicinal cannabis” includes all cannabis products taken in any form, including semi-synthetic or synthetic tetrahydrocannabinoids (eg, dronabinol). Studies that investigate medicinal cannabis in addition to other interventions will be included. The term “symptoms” includes both the core symptoms of ASD (eg, impairments in communication) and the associated symptoms of ASD (eg, behavioral symptoms, such as irritability or aggression). The term “outcomes” refers to changes in ASD symptoms, measured by validated or unvalidated tools or scales. The term “adverse event” refers to any undesirable experience associated with the use of medicinal cannabis during the treatment period.

**Context**

We will include studies undertaken in any context (hospital or community) and in any geographic location.
Types of sources
This review will consider all published or unpublished studies that investigate the use of medicinal cannabis in ASD. Due to the expectation that there is limited evidence, we will include all types of studies with data available, including randomized controlled trials, observational studies, retrospective chart reviews, case series and case reports, and qualitative studies. We will include studies published in any format, including clinical trial registry records, conference abstracts, and research letters. We will exclude literature reviews that do not include their own primary data, such as narrative reviews.

Methods
Search strategy
We will employ a three-stage search methodology, as described by JBI. An initial limited search of MEDLINE and Google Scholar was undertaken to identify articles that met the inclusion criteria. The titles and abstracts of these studies, along with articles already identified by the research team, were used to identify keywords and the indexing terms. These keywords and index terms were used to create a search that will be translated to all databases. See Appendix I for our full MEDLINE search.

We will search MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), PsycINFO (EBSCO), Web of Science, and Google Scholar. To locate gray literature, we will search clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, EU Clinical Trials Register, OpenTrials), theses and dissertations (Networked Digital Library of Theses and Dissertations, ProQuest Dissertations and Theses Global, Open Access Theses and Dissertations), and conference proceedings (PapersFirst, Proceedings). We will also search the websites of Charlotte’s Web CBD products, GW Pharmaceuticals, and the producers currently licensed in Canada to sell or produce cannabis oil. No language or date restrictions will be placed on the search. The references of all included studies will be hand searched, and Google Scholar will be used to search the citing articles of each study.

Study selection
All identified studies will be uploaded to CADIMA V2.1.3 (Julius Kühn-Institut, Quedlinburg, Germany), a web-based tool for systematic reviews, and duplicates will be removed. The resulting titles and abstracts will be screened independently and in duplicate by two team members using CADIMA. A pilot with 50 titles and abstracts will be completed to test the inclusion criteria. The resulting full-text articles will then be reviewed independently and in duplicate by two team members using CADIMA. A pilot with 10 full-text papers will be completed, and should this reveal a lack of consensus, the team members will meet to better clarify the inclusion criteria. Pilots of 50 articles will continue until at least 80% consensus has been reached. Any disagreements in screening and full-text review about the relevance of a particular study will be resolved through discussion until consensus is reached. When consensus cannot be reached, a third reviewer will be consulted. The number of potential studies identified, number of abstracts reviewed, and number of full-text articles reviewed, as well as the number eliminated at each stage of the study selection process, will be documented. The results of the search and the study selection process will be reported narratively and with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-ScR) extension for scoping reviews flow diagram.

Data extraction
A data extraction form will be created using CADIMA. A draft of the fields for the data extraction form is included in Appendix II. Minimum data to be extracted from all sources includes the following: year of publication, symptoms, sample size, age, study design, duration of treatment/follow-up, product type (eg, pharmaceutical grade, non-pharmaceutical standardized extracts, non-standard, unclear), dosage, outcomes, and adverse events.

Ten articles will be used in pilots to test the data extraction form. Once the data extraction form has been finalized, two team members will independently and in duplicate extract data from each article. Any disagreements will be discussed and resolved through consensus.

Data analysis and presentation
The extracted data will be presented as a narrative synthesis and in tabular form in a manner that aligns with the objectives of this scoping review. A narrative summary will accompany the tabulated results and will describe how the results relate to the review’s objective and questions.
SYSTEMATIC REVIEW PROTOCOL

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References


Appendix I: Search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
<1946 to October 25, 2019>

1 1 autism spectrum disorder/ or asperger syndrome/ or autistic disorder/ or child development disorders, pervasive/ (33,159)
2 (autis*/ or ASD or asberger* or PDD* or pervasive development disorder* or childhood disintegrative disorder* or CDD or Heller* syndrome or disintegrative psychosis).tw,kf. (55,661)
3 1 or 2 (59,561)
4 Cannabis/ (8699)
5 (cannabi*/ or bhang* or ganja* or hashish or hemp* or mari#uana*or Indica or charas or canna-
dor).tw,kw. (33,998)
6 Cannabinoids/ (7157)
7 Cannabidiol/ (1416)
8 (epidiolex or gwp 42003p or gwp42003p or nabitiolex or methylcannabidiol or dimethylcannabi-
diol).tw,kw. (38)
9 Dronabinol/ (6773)
10 (9?ene?tetrahydrocannabinol* or dronabinol* or marinol* or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or qcd 84924 or syndros or tetranabinex).tw,kw. (9260)
11 Terpenes/ (15,841)
12 (isoprenoids or terpen*or monoterpen*).tw,kw. (1634)
13 Marijuana Smoking/ (4542)
14 Cannabinol/ (225)
15 cannabino*.tw,kw. (601)
16 (nabilone or cesamet* or compound 109514 or cpd 109514 or cpd109514 or lilly 109514 or lilly109514 or nabiximol* or Sativex).tw,kw. (505)
17 ganka.tw,kw. (4)
18 Medical Marijuana/ (1024)
19 cbd.tw,kw. (6349)
20 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (66,206)
21 3 and 20 (116)
# Appendix II: Data extraction form

<table>
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<th>Publication</th>
<th>Year</th>
<th>Symptoms treated</th>
<th>Sample size</th>
<th>Age</th>
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*Pharmaceutical grade, non-pharmaceutical standardized extracts, non-standard, unclear.*