Received: 26 November 2020 | Revised: 3 August 2021 | Accepted: 11 August 2021

DOI: 10.1111/cch.12909

WILEY

REVIEW ARTICLE

Medicinal cannabis in children and adolescents with autism spectrum disorder: A scoping review

Sarah Fletcher[1] | Colleen Pawliuk[2] | Angie Ip[2,3] | Linda Huh[2] | S. Rod Rassekh[2] | Tim F. Oberlander[2,3] | Harold Siden[2,4]

[1]MD Undergraduate Program, University of British Columbia, Vancouver, British Columbia, Canada

[2]Department of Paediatrics, BC Children's Hospital/University of British Columbia, Vancouver, British Columbia, Canada

[3]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada

[4]Canuck Place Children's Hospice, Vancouver, British Columbia, Canada

Correspondence
Hal Siden, Department of Pediatrics, BC Children's Hospital, F612—4480 Oak Street, Vancouver, BC V6H 3N1, Canada.
Email: hsiden@bcchr.ca

Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental condition estimated to affect 1 in 66 children in Canada and 1 in 270 individuals worldwide. As effective therapies for the management of ASD core and associated symptoms are limited, parents are increasingly turning to clinicians for advice regarding the use of medicinal cannabis to manage behavioural disturbances.

Objective: The objective of this scoping review was to identify and map symptoms, outcomes and adverse events related to medicinal cannabis treatment for ASD-related behaviours.

Methods: Ovid MEDLINE, Embase, CINAHL, PsycInfo, Web of Science Core Collection, Google Scholar and grey literature sources were searched up to 5 January 2020 for studies. Included studies met the following criteria: (1) investigate the use of medicinal cannabis, (2) at least 50% participants had ASD, (3) at least 50% of the study population was 0–18 years old and (4) any study design (published or unpublished).

Results: We identified eight completed and five ongoing studies meeting the inclusion criteria. All studies reported substantial behaviour and symptom improvement on medicinal cannabis, with 61% to 93% of subjects showing benefit. In the three studies reporting on concomitant psychotropic medication usage and with cannabis use, up to 80% of participants observed a reduction in concurrent medication use. Adverse events related to cannabis use were reported in up to 27% of participants related, and two participants had psychotic events.

Conclusions: Early reports regarding medicinal cannabis in paediatric ASD symptom management are presented as positive; the evidence, however, is limited to very few retrospective cohort and observational studies. Evidence of safety and efficacy from prospective clinical trials is needed.

KEYWORDS
anxiety, autism spectrum disorder, behaviour, communication, hyperactivity

Abbreviations: ABC, Aberrant Behaviour Checklist; ADHD, attention deficit hyperactivity disorder; APSI, Autism Parenting Stress Index (APSI); ASD, autism spectrum disorder; ATEC, Autism Treatment Effectiveness Checklist; CBD, cannabidiol; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; HSQ-ASD, Home Situations Questionnaire–Autism Spectrum Disorder; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized control trial; SSRI, selective serotonin reuptake inhibitor; THC, Δ^9-tetrahydrocannabinol.

1 | 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 1 in 66 children and youth ages 5–17 have been diagnosed with ASD (Public Health Agency of Canada, 2018), whereas in the United States, approximately 1 in 54 children have been identified as having ASD (Maenner et al., 2020). ASD is characterized by deficits in social communication and social interaction, as well as restricted, repetitive patterns of behaviour, interests and activities. The concept of a spectrum disorder, such as ASD, implies wide variability in the manifestation and functional impact of the disorder among individuals with the disorder. To date, there are limited effective therapies targeting the core symptoms of ASD, and existing interventions and treatments have focused on behavioural strategies that facilitate learning and skill acquisition and improve functional skills and quality of life (Anagnostou et al., 2014). Behavioural intervention is the current standard of care for individuals with ASD (Anagnostou et al., 2014). Currently, there are no pharmacological approaches that target the core symptoms of ASD. Only a handful of medications have been found to be effective for reducing specific associated symptoms of ASD. Two atypical antipsychotics, risperidone and aripiprazole, are approved for treatment of irritability in children and adolescents with ASD (Anagnostou et al., 2014). Other medications, such as attention deficit hyperactivity disorder (ADHD) medications and melatonin, have shown benefit towards reducing specific associated symptoms of ASD, such as hyperactivity and sleep disturbances, respectively (Anagnostou et al., 2014). However, a lack of efficacy and unwanted side effects often reduce prolonged use. Recently, public and scientific attention has turned to the use of medicinal cannabis as a potential treatment for symptomatic management of the behavioural symptoms that frequently occur in children with ASD.

The recent expansion of medicinal cannabis research parallels increasing legalization of both medicinal and recreational cannabis. At the same time, parents have begun seeking information about the utility of medicinal cannabis to treat their children with ASD and other conditions, and reports of potential efficacy have shown up in mainstream media (Gibbard et al., 2021; Miles, 2012). Currently, there is limited research available on medicinal cannabis in general, but there is low-to-moderate evidence for use of medicinal cannabis for a limited list of conditions, including chronic pain, nausea and vomiting from chemotherapy, spasticity due to multiple sclerosis or spinal cord injury, Tourette's syndrome and sleep disorders (Whiting et al., 2015). In the paediatric population specifically, there is good evidence that cannabidiol products are beneficial in reducing seizures in children with specific subtypes of refractory epilepsy (Elliott et al., 2019).

Cannabis refers to a plant of the genus Cannabis, of which two species, *Cannabis sativa* and *Cannabis indica*, are the most common. The two primary components of medical relevance are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the compound responsible for the psychoactive component of cannabis, whereas CBD has opposing mechanisms and generally is thought to balance the effects of THC. Both compounds have been investigated individually and together for their efficacy as medical treatment.

Key Messages

- The studies described here show possible benefit from the use of medical cannabis in ASD, but due to the current evidence consisting of a few retrospective cohort and observational studies, and to high discontinuation rates within those studies, more work must be done.
- Treatment with medicinal cannabis was generally well tolerated, but concerns with psychiatric adverse events warrants further investigation.
- High variability in product type, dose and CBD:TCH ratio was seen across the studies, and more research is needed to determine optimal parameters of treatment.

Alterations in the body's endocannabinoid system have been implicated in children with ASD. Animal models of ASD have found alterations in the endocannabinoid signalling system (Kerr et al., 2013; S. Onaivi et al., 2011; Zamberletti et al., 2017), and additional animal studies have shown that enhancement of endocannabinoid signalling in mouse models corrects social impairment (Wei et al., 2016). Further, clinical studies have shown changes in cannabinoid receptor expression in peripheral blood cells of children with ASD and that endogenous endocannabinoid serum levels are altered in children with ASD (Karhson et al., 2018; Siniscalo et al., 2013). This body of work provides a biological and chemical background suggesting that medicinal cannabis' influence on ASD symptoms should be further explored.

Previous reviews have examined the evidence for medicinal cannabis in treating medical conditions in paediatric populations (Pawliuk et al., 2020; Wong & Wilens, 2017). A 2020 systematic review of cannabinoids in ASD highlighted significant knowledge gaps but did not focus on a paediatric population (Fusar-Poli et al., 2020). There remains significant concerns about the safety of medicinal cannabis, especially in children who have a developing brain that may be vulnerable to the effects of cannabis (Rieder, 2016). Previous studies on the recreational use of cannabis in youth have highlighted potential side effects such as impacts on memory and executive function (Schweinsburg et al., 2008) and increased risk of schizophrenia (Moore et al., 2007). As a result, policy currently reflects this substantial concern of harm. The American Academy of Pediatrics position statement on cannabis, released in 2015, states that their organization does not support the use of medicinal cannabis due to insufficient efficacy evidence and a high risk of harm to children and youth (American Academy of Pediatrics, 2019). On a similar note, the Canadian Pediatric Society has a position statement on medicinal cannabis in children that was published in 2016, stating that there is only sufficient evidence to recommend usage in epilepsy, and on a case-by-case basis in exceptional circumstances for other conditions (Rieder, 2016).

At present, although families and healthcare providers alike may be considering the potential use of medicinal cannabis as an approach to managing ASD-related symptoms, there is low scientific evidence for benefit and safety. This raises a critical and urgent need for a synthesis of current information regarding current evidence for medicinal cannabis to guide evidence informed clinical practice and prospective clinical research. As children/youth with ASD typically are unable to access cannabis without medical prescription, such evidence is particularly needed where the impact of cannabis on early brain development are uncertain and are a key concern for parents and clinicians. Thus, the objective of this scoping review is to identify and map the outcomes, adverse events and symptoms of ASD that may be treated by medicinal cannabis.

2 | METHODS

2.1 | Search strategy

We employed a three-stage search methodology, as described by the Joanna Briggs Institute (Peters et al., 2017). 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 in each database were analysed. These keywords and index terms were used to create a search that was also translated to all databases. We published an open-access protocol for this review (Fletcher et al., 2021).

We searched MEDLINE (OVID; 1946–2020), Embase (OVID; 1974–2020), CINAHL (EBSCO; 1982–2020), PsycInfo (EBSCO; 1597–2020), Web of Science Core Collection (1900–2020) and Google Scholar from database inception until 5 January 2020. To locate grey literature, we searched clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Platform, EU Clinical Trial Register and Open Trials), theses and dissertations (Networked Digital Library of Theses and Dissertations, ProQuest Dissertations and Theses Global and Open Access Theses and Dissertations) and conference proceedings (PapersFirst and Proceedings). We also searched the websites of Charlotte's Web, GW Pharmaceuticals and the 49 producers currently licensed in Canada to sell or produce cannabis oil. We did not limit our search by language or by publication date. The references of all included studies were hand searched, and Google Scholar was used to search the citing articles of each study.

2.2 | Study inclusion

Studies included in our scoping review were required to meet the following inclusion criteria: (1) at least 50% of the participants had a diagnosis of ASD or the ASD data were reported separately, (2) at least 50% of the study population was 0–18 years old or paediatric data were reported separately, (3) investigated the use of medicinal cannabis and (4) any study design, including ongoing studies. Where ASD and/or paediatric data were reported separately, we utilized only this data in our analysis. For the purposes of this study, we considered 'medicinal cannabis' to encompass all cannabis products taken in any form, including synthetic or semisynthetic cannabinoids (such as dronabinol).

2.3 | Study selection and data extraction

All identified studies were uploaded to CADIMA, a web-based tool for systematic reviews and evidence maps (Unger et al., 2020), and duplicates were removed. The resulting titles and abstracts were screened independently and in duplicate by two team members. First, we conducted a pilot with 50 references to test the inclusion criteria then proceeded to screen the remaining studies. The resulting full-text articles were then reviewed independently and in duplicate by two team members. Any disagreements in screening and full-text review about the relevance of a particular study were resolved through discussion until consensus was reached. Data extraction was performed using CADIMA independently and in duplicate. The data extracted from all sources included the year of publication, percentage of participants with ASD, sample size, age, study design, duration of treatment/follow-up, product type and preparation, daily dosage, measures, outcomes, adverse events and discontinuation rates. We further categorized the type of cannabis product investigated into (1) pharmaceutical grade products that under government drug production guidelines, are produced through a method of extraction or synthesis that results in a highly purified form of cannabinoid with minimal by-products; (2) nonpharmaceutical standardized extracts that follow a natural products regulatory framework, such as the Health Canada, to produce extracts with known CBD and THC concentrations; (3) non-standardized products with CBD and THC concentrations that are not reliably and/or transparently tested, including homemade or 'artisanal' products; or (4) unknown, where studies did not, or could not, report the type of cannabis product used. For ongoing studies, we extracted the year, trial ID, study design, estimated date of completion, estimated enrolment, eligibility criteria, intervention(s) (including dose used where available) and the period of study. For studies with projected recruitment complete at the point of data extraction, we contacted the study authors to determine if data were available for that study. The process of and results of the search are reported narratively using the PRISMA extension for scoping reviews (Tricco et al., 2018).

3 | RESULTS

Our search identified 1930 references, which was reduced to 1562 when duplicates were removed. During title and abstract screening, 1291 records were excluded for not meeting the inclusion criteria. The remaining 271 records underwent full-text review and 255 were excluded for the following reasons: not a research study ($n = 111$), wrong study population ($n = 98$), did not use medicinal cannabis

($n = 32$), full text not available ($n = 10$), full-text duplicate ($n = 3$) and no primary data or summary statistics present ($n = 2$). The remaining 15 reports were included in the review. Two reports were abstract presentations of other reports (one full-text article and one ongoing study), leaving a total of 13 studies to include in our qualitative synthesis. This includes eight completed studies and five ongoing trials. See Figure 1 for the PRISMA flow diagram and the Data S1 for our search strategies in each database and Data S2 for a list of all excluded records.

3.1 | Study design and characteristics

The eight completed studies were published from 2006 to 2019, with six of them (80%) published from 2017 onwards (Aran et al., 2018, 2019; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Gaillard, 2019; Kruger & Christophersen, 2006; Kuester et al., 2017). The sample sizes ranged from 1 to 183 (total $n = 253$), and all participants were diagnosed with ASD in all but one of the studies. The studies included participants from age 26 months to 18 years; three studies also had participants above age 18. Most studies did not report severity of symptoms, except Aran et al. that reported all participants had severe disruptive behavioural problems (Aran et al., 2018, 2019). The studies included four observational studies, two retrospective reviews and two case studies. The period of study ranged from 31 days to 2 years. Two studies used a pharmaceutical grade product, three studies used nonpharmaceutical standardized extracts, one study used artisanal extracts and for the remaining two studies, the cannabis product classification was unknown.

3.2 | Medicinal cannabis product and dosages

The majority of studies (5; 62.5%) used extracts reported to have a high CBD:THC ratio (three with a 20:1 CBD:THC ratio, one with a 75:1 CBD:THC ratio and one with a ~200:1 CBD:THC ratio), with another two studies using dronabinol, a synthetic form of THC, and one study that included balanced CBD:THC extracts, as well as high CBD and high THC extracts (Table 1). There was variation in the dosages used. Of the studies reporting CBD and/or THC dosage in units of mg/kg/day, average CBD doses ranged from 1.8 to 6.45 mg/kg/day (Aran et al., 2019; Fleury-Teixeira et al., 2019), and average doses of THC ranged from 0.22 to 0.29 mg/kg/day (Aran et al., 2019). Of studies reporting total daily doses of CBD and/or THC, average CBD doses ranged from 60 to 90 mg/day (Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Gaillard, 2019), and average THC doses ranged from 4 to 7 mg/day (Barchel et al., 2019;

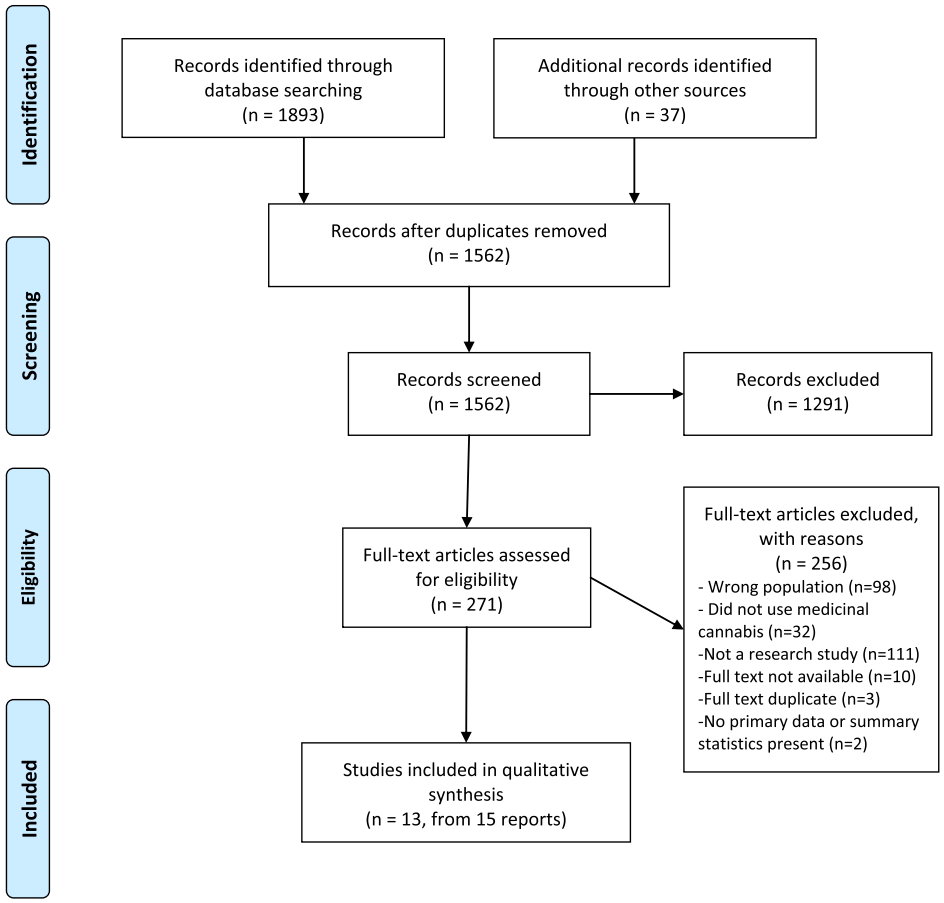

FIGURE 1 PRISMA flow diagram showing the results of the systematic search and the number of articles included and excluded at each stage

TABLE 1 Study characteristics of included completed studies

Author (date)	Sample size	% with autism	Age	Design	Length of study	Preparation; product
Aran et al. (2018) Aran et al. (2019)	57	100%	5–17.5 years	Retrospective feasibility study	7–13 months	Nonpharmaceutical standardized. Whole plant extract in olive oil, CBD:THC 20:1; given sublingually. If ineffective, lower ratios tried, up to 6:1 CBD:THC.
Barchel et al. (2019)	53	100%	4–22 years	Open-label observational study	31 to 588 days (median 66)	Nonpharmaceutical standardized. Cannabidiol oil, 30% concentration, 20:1 CBD:THC
Bar-Lev Schleider et al. (2019)	188 (93 for 6 month outcome data)	100%	Mean 12.9 ± 7 years	Prospective observational study	6 months	Unknown. Sublingual oil, 30% CBD and 1.5% THC (20:1 CBD:THC)
Fleury-Teixeira et al. (2019)	15	100%	6–17 years	Open-label observational	6–9 months	Nonpharmaceutical standardized. Cannabis extract in oral capsules; ~75:1 CBD:THC
Gaillard (2019)	1	100	5 years	Case study	2 years	Artisanal Hemp-extracted CBD with 0.005% THC; given as sublingual oil
Kruger and Christophersen (2006)	10	50%	13–16 years	Open-label prospective	6 months	Pharmaceutical. Dronabinol
Kuester et al. (2017)	21	100%	26 months to 22 years	Retrospective review	3–12 months	Unknown. Sublingual whole plant extract; ratio not controlled (72% balanced CBD:THC, 19% high CBD, 9% high THC)
Kurz and Blaas (2010)	1	100%	6 years old	Case study	6 months	Pharmaceutical. Dronabinol drops (dissolved in sesame oil)

TABLE 1 Continued

Author (date)	Daily dose	Measures	Findings	Adverse events	Discontinuation rates
Aran et al. (2018) Aran et al. (2019)	For three doses ($n = 44$): CBD: 3.8 ± 2.6 mg/kg THC: 0.29 ± 0.22 mg/kg For two doses ($n = 16$): CBD: 1.8 ± 1.6 mg/kg THC: 0.22 ± 14 mg/kg	Symptom severity and QoL scales	Considerable improvement in behaviour problems (61%), anxiety (39%), communication problems (47%). Concomitant medications: 33% received fewer or lower doses, 24% stopped entirely	Sleep disturbances (14%), restlessness (9%), nervousness (9%), loss of appetite (9%), GI symptoms (7%), unexplained laugh (7%), mood changes (5%), fatigue (5%), nocturnal enuresis (3.5%), gain of appetite (3.5%), weight loss (3.5%), weight gain (3.5%), dry mouth (3.5%), tremor (3.5%), sleepiness (2%), anxiety (2%), confusion (2%), cough (2%) Serious: Psychotic event (1 participant)	27% (3 of whom were excluded from analysis) 1—Unable to give oil 3—Side effects 5—Low efficacy 7—Low efficacy and side effects
Barchel et al. (2019)	Median dose (IQR): CBD: 90 (45–153) mg THC: 7 (4–11) mg	4 ASD comorbidity symptoms: hyperactivity, sleep, self-injury, anxiety	Overall: 75% improved, 22% no chance, 4% worsened.	Somnolence (12), appetite decrease (6), appetite increase (4), insomnia (2), abnormal response to temperature (2), eye blinking (2),	5 total (9%) 2—Low efficacy 3—Changed medical cannabis supplier or license expired

(Continues)

TABLE 1 (Continued)

Author (date)	Daily dose	Measures	Findings	Adverse events	Discontinuation rates
			Improvement by symptom: 68% hyperactivity, 68% self-injury, 71% sleep, anxiety 47%	diarrhoea (2), hair loss (1), nausea (1), confusion (1), acne (1), palpitations (1), urinary incontinence (1), eye redness (1), constipation (1)	
Bar-Lev Schleider et al. (2019)	Average dose: CBD: 79.5 ± 61.5 mg THC: 4.0 ± 3.0 mg If insomnia present: Additional 5 ± 4.5 mg THC in evening	Symptom improvement QoL, mood, ability to perform ADLs	30% significant improvement, 53% moderate improvement, 6% slight improvement, 9% no change. Statistically significant increase in QoL, positive mood, ADLs and sleep. Concomitant medication use: 34% decrease	Restlessness (6), sleepiness (3), psychoactive effect (3), increased appetite (3), digestion problem (3), dry mouth (2), lack of appetite (2)	23 total discontinued (12%); 12 due to no therapeutic effect, 5 due to side effects, 6 unknown
Fleury-Teixeira et al. (2019)	Final dose: CBD: 3.75 to 6.45 mg/kg	Symptom severity: ADHD, behaviour, motor, autonomy, communication and social interaction, cognition, sleep, seizures	93% had improvement in at least one symptom category, 47% had improvement in 4+ symptom categories Concomitant medications: 80% decreased or stopped entirely	Out of patients that completed: Sleepiness (3), irritability (2), diarrhoea (1), increased appetite (1), conjunctival hyperaemia (1), increased body temperature (1), nocturia (2). Patients that stopped: insomnia, irritability, increased HR, worsening psycho-behavioural crisis	3 stopped within 1 month due to adverse events (excluded from analysis) 1 stopped at 6 months due to worsening of psycho-behavioural crisis Total = 27%
Gaillard (2019)	60-mg CBD	Symptom severity and participation in activities	Reduced need from 1:1 support to full school without support, improved sleep, focus, attention, reduced anxiety and problem behaviours	None reported.	N/A
Kruger and Christophersen (2006)	0.14–0.36 mg/kg	Improvement, side effects	70% had significant improvement in self-injurious behaviour and overall mood	Increased appetite (2 out of 7), agitation (2 out of 10)	3 (30%); 2 due to increased agitation, 1 due to change in living situation
Kuester et al. (2017)	Not reported	Symptom severity scales	67% had significant improvements in at least one of the core symptoms of ASD	Well tolerated. More agitation (2) patients and irritability (1) resolved by changing strain	Not reported
Kurz and Blaas (2010)	3.72 mg	Symptom severity scales	Improvement in hyperactivity, lethargy, irritability, stereotypic behaviour, inappropriate speech	None reported	N/A

Bar-Lev Schleider et al., 2019) in patients with an age range of 2–22 years. Of the studies that used dronabinol, one study reported a dose range of 0.14–0.36 mg/kg/day (Kruger & Christophersen, 2006), and one study reported a dosage of 3.72 mg (Kurz & Blaas, 2010). One study did not report dosage (Kuester et al., 2017).

3.3 | Outcome measures

All eight included studies completed at the time of this review reported a majority of participants with ASD showing improvement after treatment with medicinal cannabis. There is variability in how the included studies assessed response to medicinal cannabis treatment. Four studies used one or more standardized assessment tools (Aran et al., 2019; Gaillard, 2019; Kuester et al., 2017; Kurz & Blaas, 2010), which included the Autism Treatment Effectiveness Checklist (ATEC), the Aberrant Behaviour Checklist (ABC), the Autism Parenting Stress Index (APSI), Clinical Global Impression of Improvement (CGI-I), the Clinical Global Impression of Severity (CGI-S) and the Home Situations Questionnaire–Autism Spectrum Disorder (HSQ-ASD). Two studies used unvalidated questionnaires to capture parent reports of improvement (Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019), and one study used a verbal parent report (Barchel et al., 2019). One study did not report the assessment tool used (Kruger & Christophersen, 2006).

3.4 | Benefits

Of the four observational studies, the overall rates of some degree of improvement in behaviour and/or symptoms ranges from 70% to 93% of participants. Both retrospective reviews showed improvement rates in behaviours (Aran et al., 2019) or core ASD symptoms (Kuester et al., 2017) of 61% and 67%, respectively. The two case studies included in this scoping review both reported improvement in challenging behaviours and other symptoms, and one case study (Gaillard, 2019) observed a reduction in the amount of support services the child required following initiation of medicinal cannabis treatment.

Three studies (Aran et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019) reported on the changes to concomitant medication use for ASD symptoms (including medication classes such as benzodiazepines, selective serotonin reuptake inhibitors [SSRIs], stimulants and antipsychotics) following commencement of medicinal cannabis treatment. Aran et al. (2019) found that, of participants taking concomitant medication, 33% decreased their total daily dose of other medications and 24% stopped completely. Bar-Lev Schleider et al. (2019) observed that 34% of those participants taking concomitant medications had a decrease once started on medicinal cannabis treatment. In Fleury-Teixeira et al. (2019), 80% of participants taking concomitant medications decreased or stopped those medications during the study.

3.5 | Symptoms assessed

The completed studies showed some overlap in the core and comorbid symptoms of ASD assessed (Table 2). Common symptoms specifically reported as improved following medicinal cannabis treatment were anxiety (three studies; Aran et al., 2019; Barchel et al., 2019; Bar-Lev Schleider et al., 2019), behavioural challenges (four studies; Aran et al., 2019; Fleury-Teixeira et al., 2019; Gaillard, 2019; Kuester et al., 2017), cognitive deficits (three studies; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Gaillard, 2019), communication challenges (four studies; Aran et al., 2019; Gaillard, 2019; Kuester et al., 2017; Kurz & Blaas, 2010), hyperactivity (four studies; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Kurz & Blaas, 2010), mood (two studies; Bar-Lev Schleider et al., 2019; Kruger & Christophersen, 2006), rage (two studies; Barchel et al., 2019; Bar-Lev Schleider et al., 2019), repetitive behaviours (two studies; Kuester et al., 2017; Kurz & Blaas, 2010), self-injury (two studies; Barchel et al., 2019; Kruger & Christophersen, 2006), seizures (three studies; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Kuester et al., 2017) and sleep challenges (four studies; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Kuester et al., 2017). Of the four studies that reported numerical outcomes (% of participants improved) for specific symptoms, although not all studies reported on all symptoms, improvement was seen in anxiety (three studies, 39% to 89%; Aran et al., 2019; Barchel et al., 2019; Bar-Lev Schleider et al., 2019), behavioural challenges (two studies, 53% to 61%; Aran et al., 2019; Fleury-Teixeira et al., 2019), communication (two studies, 47% to 80%; Aran et al., 2019; Fleury-Teixeira et al., 2019), hyperactivity (three studies, 68% to 90%; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019) and sleep (three studies, 71% to 80%; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019). Although not a focus of this review, it is worth noting that two studies reported numerical results of seizures, both with 100% of participants showing improvement (Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019).

3.6 | Adverse events

Six of the eight completed studies reported adverse events. Table 3 shows the combined data for adverse events for these six studies (total number of participants = 253). The most commonly reported adverse events were somnolence (19 participants, 7.5%), decreased appetite (13 participants, 5.1%), gastrointestinal symptoms (12 participants, 4.7%), increased appetite (12 participants, 4.7%), restlessness (11 participants, 4.3%) and sleep disturbances (11 participants, 4.3%). Two studies reported one patient each with psychiatric effects—one had a worsening psycho-behavioural crisis (Fleury-Teixeira et al., 2019), and the other had a psychotic event (Aran et al., 2019)—while taking medicinal cannabis, both of which led to the discontinuation of treatment. One of these patients was taking a THC dose of

TABLE 2 Symptoms assessed

Symptom	Number of studies reporting (any results)	Number of studies reporting (numerical results)	Range of numerical results (% of participants improved)
Anxiety	3 (Aran et al., 2019; Barchel et al., 2019; Bar-Lev Schleider et al., 2019)	3 (Aran et al., 2019; Barchel et al., 2019; Bar-Lev Schleider et al., 2019)	39% to 89%
Behavioural challenges	4 (Aran et al., 2019; Fleury-Teixeira et al., 2019; Gaillard, 2019; Kuester et al., 2017)	2 (Aran et al., 2019; Fleury-Teixeira et al., 2019)	53% to 61%
Cognitive deficits	3 (Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Gaillard, 2019)	0	n/a
Communication challenges	4 (Aran et al., 2019; Gaillard, 2019; Kuester et al., 2017; Kurz & Blaas, 2010)	2 (Aran et al., 2019; Fleury-Teixeira et al., 2019)	47% to 80%
Hyperactivity	4 (Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Kurz & Blaas, 2010)	3 (Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019)	68% to 90%
Mood	2 (Bar-Lev Schleider et al., 2019; Kruger & Christophersen, 2006)	0	n/a
Rage	2 (Barchel et al., 2019; Bar-Lev Schleider et al., 2019)	0	n/a
Repetitive behaviours	2 (Kuester et al., 2017; Kurz & Blaas, 2010)	0	n/a
Self-injury	2 (Barchel et al., 2019; Kruger & Christophersen, 2006)	0	n/a
Seizures	3 (Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Kuester et al., 2017)	2 (Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019)	100%
Sleep challenges	4 (Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019; Kuester et al., 2017)	3 (Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Fleury-Teixeira et al., 2019)	71% to 80%

0.72 mg/kg/day (Aran et al., 2019), which was on the high side of reported doses in that study, and the dosage THC of the other patient was not reported (Fleury-Teixeira et al., 2019). The studies with psychiatric adverse events used nonpharmaceutical standardized products at a ratio of CBD:THC of 75:1 and 20:1 (which was reduced to 6:1 if ineffective), respectively.

3.7 | Discontinuation rates

Five studies reported on discontinuation rates. The discontinuation rates ranged from 9% to 27% and included discontinuation reasons of side effects, worsening symptoms, low efficacy and inability to give the medication (see Table 1).

3.8 | Ongoing study design, characteristics and dosage

A total of five ongoing studies examining medicinal cannabis in the paediatric ASD population were identified by our search. This included two randomized control trials (RCTs), two open-label studies and one cohort registry. Three of the studies are taking place in the United States, one in Israel and one in Australia, with estimated sample sizes ranging from 30 to 150 participants. All included studies are focusing on children with ASD from as young as 4 years old, up to age 21 in some studies. Each study is using a different medicinal cannabis product, with study periods lasting from 6 weeks to 1 year. Of studies investigating CBD-containing products, dosages ranged from 1 to 10 mg/kg/day for two studies investigating oral CBD (Aran, 2018; Castellanos, 2020) and 250 to 500 mg/day for one study investigating transdermal CBD application (Heussler, 2019). One study investigating cannabidivarin reported a 10-mg/kg/day dose (Hollander, 2019). One study did not report a dosage (Diliberto et al., 2018; Zuppa, 2020). Table 4 shows the characteristics of ongoing studies.

4 | DISCUSSION

This scoping review presented outcomes from the eight completed studies reporting on the use of medicinal cannabis to manage symptoms in children and youth with ASD. These studies were characterized by variations in study designs (observational studies, retrospective reviews and case studies), sample sizes, outcome measures, duration of treatment and nature of side effects. All studies reported improvement in ASD-related behavioural symptoms after starting on medicinal cannabis treatment. This included improved

TABLE 3 Pooled adverse event data

Adverse event	Frequency (%); $n = 251$
Somnolence	19 (7.6%)
Decreased appetite	13 (5.2%)
Gastrointestinal symptoms	12 (4.8%)
Increased appetite	12 (4.8%)
Restlessness	11 (4.4%)
Sleep disturbances	11 (4.4%)
Anxiety and nervousness	6 (2.4%)
Irritability	5 (2.0%)
Urinary incontinence (including nocturnal enuresis)	5 (2.0%)
Agitation	4 (1.6%)
Dry mouth	4 (1.6%)
Unexplained laugh	4 (1.6%)
Fatigue	3 (1.2%)
Mood changes	3 (1.2%)
Abnormal response to temperature	2 (0.8%)
Confusion	2 (0.8%)
Eye blinking	2 (0.8%)
Eye redness	2 (0.8%)
Tremor	2 (0.8%)
Weight gain	2 (0.8%)
Weight loss	2 (0.8%)
Worsening psychiatric symptoms	2 (0.8%)
Acne	1 (0.4%)
Cough	1 (0.4%)
Hair loss	1 (0.4%)
Increased body temperature	1 (0.4%)
Increased heart rate	1 (0.4%)
Palpitations	1 (0.4%)

anxiety, communication, hyperactivity and sleep disturbances. Moreover, there was great heterogeneity in product source, chemical composition and dosing, as well as the outcome measures used to assess improvement. Most studies did not use standardized symptom scores, instead gathered data with internally developed surveys or global assessment scales. This heterogeneity in outcome measures for ASD research has recently been characterized in a systematic review (Provenzani et al., 2020). These factors will make establishing effect size and power calculations difficult for future RCTs.

Of note, none of the identified completed studies were RCTs. Although retrospective and observational research studies are beneficial, they provide a lower quality of evidence than RCTs. Of particular note in the case of medicinal cannabis efficacy, the results reported in these observational and retrospective studies could be skewed by recall bias; a study looking at the efficacy of medicinal cannabis for refractory paediatric epilepsy found that improvement rates were higher (47% vs. 22%) among families who had moved to access medicinal cannabis compared with those already living in an area where they could access medicinal cannabis (Press et al., 2015). This finding suggests the presence of recall bias when asking parents or caregivers to assess improvement following medicinal cannabis, which is a limitation of retrospective studies and those studies which rely on parent reports and do not use validated tools to assess patient improvement.

The completed studies indicated that up to 27% of patients (total from all studies $n = 253$) reported adverse events, although these side effects were generally mild. Of note, there were two patients who experienced psychotic or behavioural symptoms that led to immediate cessation of the treatment (Aran et al., 2019; Fleury-Teixeira et al., 2019). The concern regarding the use of cannabis, particularly with high THC content, and a well-established link to psychosis and/or schizophrenia is well characterized in the literature (Rieder, 2016), although the studies that found these correlations were looking at the use of recreational cannabis (Moore et al., 2007; Schweinsburg et al., 2008). Additionally, of note is that included studies reported discontinuation rates of 9% to 27%, in part due to side effects or low efficacy of the cannabis treatment. These high discontinuation rates may have artificially inflated the rates of improvement as some studies excluded participants who discontinued from analysis. In designing future RCTs, the likely overestimation of treatment efficacy due to high discontinuation rates should be considered.

Previous literature reviews have analysed the available evidence for the use of medicinal cannabis in treating a variety of paediatric conditions (Pawliuk et al., 2020; Wong & Wilens, 2017), finding that there is substantial evidence supporting the use of medicinal cannabis in the treatment of refractory paediatric epilepsy, with limited-to-no evidence available for other paediatrics conditions. Epilepsy is a common medical comorbidity of ASD; however, no specific mention was made of the use of cannabis in individuals with epilepsy and comorbid ASD in these reviews. Our review did not focus on epilepsy or seizure symptoms but did note that two studies did report numerical results with respect to seizures in those participants with comorbid epilepsy, showing a 100% response rate with respect to seizures. These reviews also found similar concerns as identified in this review relating to adverse events. Of note, two systematic/scoping reviews looking at medicinal cannabis conducted in 2017 and 2018, respectively, did not identify or include studies with ASD, highlighting the rapidly evolving nature of work in this field.

Additionally, our review identified five ongoing clinical trials (Aran, 2018; Castellanos, 2020; Hollander, 2019; Heussler, 2019; Zuppa, 2020), and there is also the potential of other unregistered studies such as case studies and retrospective reviews that may currently be underway that should further inform the safe and efficacious use of medicinal cannabis in children with ASD. These studies included two RCTs, which would address some of the limitations of the observational and retrospective review studies identified in this scoping review, by providing a higher quality of evidence, with data less affected by parental recall bias.

One limitation of this scoping review is that our literature search of databases and grey literature was performed in January 2020; in

TABLE 4 Study characteristics of included ongoing studies

Author (date) Country Trial ID	Study design	Status Estimated enrolment Estimated completion	Eligibility criteria Interventions (dose) Period of study
Aran (2018) Israel NCT02956226	Double-blind RCT	Study competed—no data available 150 participants December 2018	Children with ASD ages 5–21 years Intervention 1: 20:1 CBD:THC extract in oil solution (1–10 mg/kg/day of CBD) Intervention 2: 20:1 99% pure CBD:THC (1–10 mg/kg/day of CBD) Intervention 3: Placebo 12 week period, crossover for additional 12 weeks
Castellanos (2020) United States NCT03900923	Open-label phase 2 clinical trial	Recruiting 30 participants January 2021	Children with ASD ages 7–17.9 years 98% pure CBD oral solution (3, 6 or 9 mg/kg/day) 6 weeks
Heussler (2019) Australia ACTRN12619000216112	Open-label study	Unknown 36 participants February 2020	Children with ASD ages 4 to <18 years Transdermal gel synthetic cannabidiol (250–500 mg/day of CBD) 14 weeks
Hollander (2019) United States NCT03202303	Double-blind RCT	Recruiting 100 participants September 2021	Children with ASD ages 5–18 years Intervention 1: Cannabidivarin (10 mg/kg/day) Intervention 2: Placebo 12 weeks
Zuppa (2020); Diliberto et al. (2018) United States NCT03699527	Prospective cohort registry	Recruitment complete—no data available 119 participants January 2020	Children and youth with ASD up to age 21 Medicinal cannabis products (dose not specified) 1 year

this emerging field, the literature may have changed since that date. It will be important to update reviews such as this one regularly in the future so that new evidence can be identified. Further, this study may also have been limited by potentially missing studies looking at the use of cannabis for other conditions (such as fragile X or epilepsy) that may have had a proportion of participants with a concurrent ASD diagnosis, especially when considering ongoing studies. We chose to focus on ASD for this review to limit the scope but recognize there is much overlap with other conditions that may be studied for the use of medicinal cannabis as well. Lastly, as this is a scoping review and we did not critically appraise the included studies, we are not able to comment on any potential risk of bias or reach conclusions on the efficacy and/or safety of medicinal cannabis for ASD. A systematic review will need to be conducted when there is more available evidence to assess efficacy and/or safety and make recommendations for treatment. This scoping review can provide guidance for other reviews on the breath of the current literature and on potentially safety concerns that should be investigated further.

5 | CONCLUSION

In summary, the use of medicinal cannabis in children and youth with ASD is an increasing area of scientific and public attention, yet to date, published research remains limited, leading to a lack of sufficient evidence for the use of medicinal cannabis as a symptomatic behavioural treatment for children and youth with ASD. The eight identified studies all found positive results in that the majority of participants improved; however, it is important to note that adverse events were also reported in up to 27% of participants. We identified five ongoing clinical studies, suggesting that in the next few years, more research will become available in this field, which will provide paediatric clinicians more of an evidence base to utilize when counselling parents on this subject. Given the heterogenetic nature of ASD and comorbid conditions, novel study designs, such as *N*-of-1 trials and placebo dose reduction designs, may be required to account for confounding factors, the placebo effect and individual variability in pharmacological metabolism. Additionally, further research will need to investigate the impact of medicinal cannabis on functional status in children and youth with ASD, as in a clinical context, changes in symptom severity may not always correlate to functional improvement. The results from early studies in this field show a need to continue further research in this area, including the currently ongoing RCTs.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Data S1 and S2.

ORCID

Colleen Pawliuk https://orcid.org/0000-0001-7507-8759
S. Rod Rassekh https://orcid.org/0000-0001-8005-2641

Tim F. Oberlander https://orcid.org/0000-0003-4781-6579
Harold Siden https://orcid.org/0000-0001-8419-8912

REFERENCES

American Academy of Pediatrics. (2019). The impact of marijuana policies on youth: Clinical, research, and legal update. *Pediatrics*, *135*(3), 584.

Anagnostou, E., Zwaigenbaum, L., Szatmari, P., Fombonne, E., Fernandez, B. A., Woodbury-Smith, M., Brian, J., Bryson, S., Smith, I. M., Drmic, I., Buchanan, J. A., Roberts, W., & Scherer, S. W. (2014). Autism spectrum disorder: Advances in evidence-based practice. *Canadian Medical Association Journal*, *186*(7), 509–519. https://doi.org/10.1503/cmaj.121756

Aran, A. (2018). Cannabinoids for behavioural problems in children with ASD (CBA). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02956226.

Aran, A., Cassuto, H., & Lubotzky, A. (2018). Cannabidiol based medical cannabis in children with autism—A retrospective feasibility study (P3.318). *Neurology*, *90*(15 Supplement), P3.318.

Aran, A., Cassuto, H., Lubotzky, A., Wattad, N., & Hazan, E. (2019). Brief report: Cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems—A retrospective feasibility study. *Journal of Autism and Developmental Disorders*, *49*(3), 1283–1288.

Barchel, D., Stolar, O., De-Haan, T., et al. (2019). Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. *Frontiers in Pharmacology*, *9*, 1521. https://doi.org/10.3389/fphar.2018.01521

Bar-Lev Schleider, L., Mechoulam, R., Saban, N., Meiri, G., & Novack, V. (2019). Real life experience of medical cannabis treatment in autism: Analysis of safety and efficacy. *Scientific Reports*, *9*, 200. https://doi.org/10.1038/s41598-018-37570-y

Castellanos, F. (2020). Cannabidiol for ASD Open Trial. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03900923.

Diliberto, M., Prodell, J., Moorthy, G., Vedar, C., Irizarry, J., & Zuppa, A. (2018). Implementation of a pediatric medical cannabis research program. *Clinical Pharmacology in Drug Development*, *7*(S1), 64.

Elliott, J., DeJean, D., Clifford, T., Coyle, D., Potter, B. K., Skidmore, B., Alexander, C., Repetski, A. E., Shukla, V., McCoy, B., & Wells, G. A. (2019). Cannabis-based products for pediatric epilepsy: A systematic review. *Epilepsia*, *60*(1), 6–19. https://doi.org/10.1111/epi.14608

Fletcher, S., Pawliuk, C., Ip, A., Oberlander, T., & Siden, H. (2021). Symptoms, adverse events and outcomes in the use of medicinal cannabis in children and adolescents with autism spectrum disorder: A scoping review protocol. *JBI Evidence Synthesis*, *19*(5), 1251–1258.

Fleury-Teixeira, P., Viegas Caixeta, F., Cruz Ramires da Silva, L., Pereira Brasil-Neto, J., & Malcher-Lopes, R. (2019). Effects of CBD-enriched *Cannabis sativa* extract on autism spectrum disorder symptoms: An observational study of 18 participants undergoing compassionate use. *Frontiers in Neurology*, *10*, 1145. https://doi.org/10.3389/fneur.2019.01145

Fusar-Poli, L., Cavone, V., Tinacci, S., Concas, I., Petralia, A., Signorelli, M. S., Díaz-Caneja, C. M., & Aguglia, E. (2020). Cannabinoids for people with ASD: A systematic review of published and ongoing studies. *Brain Sciences*, *10*(9), 572. https://doi.org/10.3390/brainsci10090572

Gaillard, J. B. (2019). Positive autism intervention with cannabidiol: A case study. *American Journal of Endocannabinoid Medicine*, *1*(1), 55–58.

Gibbard, M., Mount, D., Rassekh, S. R., & Siden, H. (2021). Family attitudes about and experiences with medical cannabis in children with cancer or epilepsy: An exploratory qualitative study. *CMAJ Open*, *9*(2), E563.

Heussler, H. (2019). Clinical study of synthetic cannabidiol in children and adolescents with autism spectrum disorder. Australian New Zealand Clinical Trials Registry. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376870

Hollander, E. (2019). Cannabidivarin (CBDV) vs placebo in children with autism spectrum disorder. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03202303

Karhson, D. S., Krasinska, K. M., Dallaire, J. A., Libove, R. A., Phillips, J. M., Chien, A. S., Garner, J. P., Hardan, A. Y., & Parker, K. J. (2018). Plasma anandamide concentrations are lower in children with autism spectrum disorder. *Molecular Autism*, *9*(1), 1–6.

Kerr, D., Downey, L., Conboy, M., Finn, D., & Roche, M. (2013). Alterations in the endocannabinoid system in the rat valproic acid model of autism. *Behavioural Brain Research*, *249*, 124–132. https://doi.org/10.1016/j.bbr.2013.04.043

Kruger, T., & Christophersen, E. (2006). An open label study of the use of dronabinol (Marinol) in the management of treatment-resistant self-injurious behavior in 10 retarded adolescent patients. *Journal of Developmental and Behavioral Pediatrics*, *27*(5), 433. https://doi.org/10.1097/00004703-200610000-00029

Kuester, G., Vergara, K., Ahumada, A., & Gazmuri, A. (2017). Oral cannabis extracts as a promising treatment for the core symptoms of autism spectrum disorder: Preliminary experience from Chilean patients. *Journal of the Neurological Sciences*, *381*(Supplement), 932–933.

Kurz, R., & Blaas, K. (2010). Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child. *Cannabinoids*, *5*(4), 4–6.

Maenner, M. J., Shaw, K. A., & Baio, J. (2020). Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2016. *MMWR Surveillance Summaries*, *68*(SS-4), 1–12.

Miles, K. (2012). Marijuana-like chemical may help autism and fragile X syndrome symptoms. The Huffington Post. https://www.huffingtonpost.ca/2012/09/27/marijuana-chemical-autism-fragile-x_n_1920320.html. Accessed September 16, 2019.

Moore, T. H., Zammit, S., Lingford-Hughes, A., et al. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet*, *370*(9584), 319–328. https://doi.org/10.1016/S0140-6736(07)61162-3

Pawliuk, C., Chau, B., Rassekh, R., McKellar, T., & Siden, H. (2020). Efficacy and safety of paediatric medicinal cannabis use: A scoping review. *Paediatrics & Child Health*, *26*(4), 228–233.

Peters, M., Godfrey, C., McInerney, P., Baldini Soares, C., Kahlil, H., & Parker, D. (2017). Chapter 11: Scoping reviews. Joanna Briggs Institute Reviewer's Manual. https://wiki.joannabriggs.org/display/MANUAL/Chapter+11%3A+Scoping+rev. Accessed October 7, 2019.

Press, C. A., Knupp, K. G., & Chapman, K. E. (2015). Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy & Behavior*, *45*, 49–52. https://doi.org/10.1016/j.yebeh.2015.02.043

Provenzani, U., Fusar-Poli, L., Brondino, N., Damiani, S., Vercesi, M., Meyer, N., Rocchetti, M., & Politi, P. (2020). What are we targeting when we treat autism spectrum disorder? A systematic review of 406 clinical trials. *Autism*, *24*(2), 274–284. https://doi.org/10.1177/1362361319854641

Public Health Agency of Canada. (2018). Autism spectrum disorder among children and youth in Canada 2018: A Report of the National Autism Spectrum Disorder Surveillance System. Ottawa, Canada. https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/autism-spectrum-disorder-children-youth-canada-2018/autism-spectrum-disorder-children-youth-canada-2018.pdf

Rieder, M. J. (2016). Canadian Pediatric Society Drug Therapy and Hazardous Substances Committee. Position statement: Is the medical use of cannabis a therapeutic option for children? *Paediatrics & Child Health*, *21*(1), 31–34. https://doi.org/10.1093/pch/21.1.31

S. Onaivi, E., Benno, R., Halpern, T., Mehanovic, M., Schanz, N., Sanders, C., Yan, X., Ishiguro, H., Liu, Q.-R., L. Berzal, A., P. Viveros, M., & F. Ali, S. (2011). Consequences of cannabinoid and

monoaminergic system disruption in a mouse model of autism spectrum disorders. *Current Neuropharmacology*, *9*(1), 209–214. https://doi.org/10.2174/157015911795017047

Schweinsburg, A., Nagel, B., Schweinsburg, B., Park, A., Theilmann, R., & Tapert, S. (2008). Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. *Psychiatry Research*, *163*(1), 40–51. https://doi.org/10.1016/j.pscychresns.2007.04.018

Siniscalo, D., Sapone, A., Giordano, C., et al. (2013). Cannabinoid receptor type 2, but not type 1 is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders. *Journal of Autism and Developmental Disorders*, *42*(11), 2686–2695.

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Annals of Internal Medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Unger, S., Kluth, R., Kecke, S., Wolck, A., Kohl, C., Haddaway, N. & Wilhelm, R. (2020). CADIMA. Julius Kuhn-Institut: Federal Research Center for Cultivated Plants. Retrieved from https://www.cadima.info/

Wei, D., Dinh, D., Lee, D., Li, D., Anguren, A., Moreno-Sanz, G., Gall, C. M., & Piomelli, D. (2016). Enhancement of anandamide-mediated endocannabinoid signaling corrects autism-related social impairment. *Cannabis and Cannabinoid Research*, *1*(1), 81–89. https://doi.org/10.1089/can.2015.0008

Whiting, P. F., Wolff, R. F., Deshpande, S., di Nisio, M., Duffy, S., Hernandez, A. V., Keurentjes, J. C., Lang, S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood, M., & Kleijnen, J. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *Journal of the American Medical Association*, *313*(24), 2456–2473. https://doi.org/10.1001/jama.2015.6358

Wong, S., & Wilens, T. E. (2017). Medical cannabinoids in children and adolescents: A systematic review. *Pediatrics*, *140*(5), e20171818. https://doi.org/10.1542/peds.2017-1818

Zamberletti, E., Marina, G., & Parolaro, D. (2017). The endocannabinoid system and autism spectrum disorders: Insights from animal models. *International Journal of Molecular Sciences*, *18*(9), 1916. https://doi.org/10.3390/ijms18091916

Zuppa, A. (2020). Medical Cannabis Registry and Pharmacology (Med Can Autism). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03699527

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Fletcher, S., Pawliuk, C., Ip, A., Huh, L., Rassekh, S. R., Oberlander, T. F., & Siden, H. (2021). Medicinal cannabis in children and adolescents with autism spectrum disorder: A scoping review. *Child: Care, Health and Development*, 1–12. https://doi.org/10.1111/cch.12909