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Medicinal and Synthetic Cannabinoids for Pediatric Patients: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

CINV	chemotherapy-induced nausea and vomiting
FDA	Food and Drug Administration
PICO	population, intervention, comparator, and outcome
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
SR	systematic review
THC	tetrahydrocannabinol

Context and Policy Issues

Cannabinoids are pharmacologically active agents extracted from the cannabis plant.[1] Cannabidiol and tetrahydrocannabinol (THC) are the most studied cannabinoids and both interact with endocannabinoid receptors in various human tissues.[1] The endocannabinoid system moderates physiological functions, such as neurodevelopment, cognition, and motor control.[2] The products naturally derived from cannabis include marijuana (dried leaves and flowers, mostly for smoking) and oral cannabinoid extracts with varying concentrations of cannabinoids, including cannabidiol and THC.[1] THC is the main psychoactive constituent and cannabidiol seems to have no psychoactive properties.[2] In addition, there are two synthetical cannabinoids approved by the Food and Drug Administration (FDA) in the United States, dronabinol and nabilone, which are molecules similar to a type of THC (δ-9-THC)[1] Nabilone is also approved in Canada.[3] Dronabinol is indicated for chemotherapy-induced nausea and vomiting in children.[1] The use of nabilone in children is not recommended.[1]

In Canada, the minimum age for cannabis consumption varies by provinces and territories, and is either 18 or 19 years.[4] A prescription is required to administer cannabinoids among children.[4] Clinically, cannabis has been used to treat children with epilepsy,[5] cancer palliation and primary treatment, chronic pain, and Parkinson disease.[6] The adverse events that clinicians need to monitor for include negative psychoactive sequelae and development of tolerance.[6] Psychoactive sequelae may be positive, such as relaxation and euphoria, or negative, such as anxiety and irritability.[2] In 2016, CADTH completed a Summary of Abstracts report on the use of cannabis in children with medical conditions such as attention deficit hyperactivity disorder, autism spectrum disorder, Tourette syndrome, epilepsy, posttraumatic stress disorder, or neurodegenerative diseases, and five non-randomized studies were identified.[7] However, there were no control groups in the five studies included in the report.[8-12] It is unclear whether there is new evidence or clinical guidance for the use of medical cannabis in children with mental health conditions, neurodegenerative diseases, or pain disorders, particularly in comparison with other possible therapies for those conditions. There is a need to review the clinical effectiveness of cannabis for pediatric care, as well as clinical guidelines.

Research Questions

1. What is the clinical effectiveness of medical cannabinoids in pediatric patients?
2. What is the clinical effectiveness of synthetic cannabinoids in pediatric patients?
3. What are the evidence-based guidelines regarding the use of medical or synthetic cannabinoids in pediatric patients?

Key Findings

One systematic review (SR) without independent literature selection or data extraction and one fair-quality randomized controlled trial (RCT) were identified. Cannabidiol and oral cannabis extracts of various dosing strategies were identified and associated with a reduction in epilepsy frequency in pediatric patients with epilepsy, based on the SR. In the RCT recruiting pediatric patients with severe complex motor disorder, the 5% oil formulation of cannabis made with two cannabidiol-to-tetrahydrocannabinol (THC) ratios (20:1 or 6:1) was associated with a reduction in spasticity, sleep difficulties, and pain and an improvement in quality of life relative to baseline with rare occurrence of adverse events.

Dronabinol was a synthetical cannabinoid identified in the SR and associated with a reduction in seizure frequency in epilepsy patients and a reduction in spasticity in patients with spasticity.

No evidence-based guidelines were identified, and no summary could be provided.

This report was limited by several factors: small sample sizes in the primary studies (several studies with fewer than 30 patients), lack of publication bias assessment, and the lack of comparability between primary studies due to the differences in the patients and the types and dosages of cannabinoids. The identified evidence for this report was limited to the following conditions: PTSD for mental health conditions, epilepsy and spasticity for neurodegenerative diseases, and neuropathic pain for pain disorders. The synthetic cannabinoid evaluated in the systematic review, Dronabinol, is not available in Canada. Therefore, this evidence may be of limited value in a Canadian clinical setting or for pediatric patients with other mental health conditions, neurogenerative diseases, or pain disorders.

Further research in the effectiveness of medicinal or synthetical cannabinoids in Canadian contexts may help to reduce uncertainty.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were medical cannabis or cannabinoids and pediatrics. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials, controlled clinical trials, or any other type of clinical trial, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and September 16, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The included studies in a CADTH Summary of Abstracts were also retrieved

for assessment.[7] The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pediatric patients (<18 years of age) with: • mental health conditions (e.g., attention deficit hyperactivity disorder, autism spectrum disorder, Tourette syndrome, epilepsy [active or refractory], posttraumatic stress disorder) • neurodegenerative diseases (e.g., multiple sclerosis, other conditions associated with dystonia and spasticity) • pain disorders (non-cancer and cancer-related)
Intervention	Q1-Q3: Medicinal cannabinoids (e.g., tetrahydrocannabinol, cannabidiol) or synthetic cannabinoids (e.g., nabilone) delivered in various formulations (e.g., oil [e.g., Avidekel oil], oral, buccal forms, ingestible, inhaled, injected)
Comparator	Q1-Q2: Any active comparator; No treatment Q3: Not Applicable
Outcomes	Q1-Q2: Clinical effectiveness (e.g., clinical benefit, symptom reduction, quality of life) Safety (e.g., tolerability, dependence and addiction, withdrawal, psychosis, behavioral changes, memory deficits, sedation) Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2 checklist[13] and randomized studies were critically appraised using the Downs and Black checklist.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 498 citations were identified in the literature search. Following screening of titles and abstracts, 484 citations were excluded and 15 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full text review. Five primary studies in a related CADTH Summary of Abstracts were retrieved for full text review.[7] Of these 20 potentially relevant articles, 18 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised one systematic review (SR) and one randomized controlled trial (RCT). Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

Systematic reviews

Wong and Wilens conducted a SR to identify any primary studies with original data on the effectiveness of cannabinoids and published the SR in 2017.[1] Multiple databases were searched in May 2017; the search date range was not provided.[1] RCTs, non-randomized studies and case reports were included in the SR.[1]

RCTs

Libzon et al. conducted a single-centre RCT.[2]

Country of Origin

Systematic reviews

The first author of the SR by Wong and Wilens was based in the USA.[1]

RCTs

The first author of the RCT by Libzon et al. was based in Israel.[2]

Patient Population

Systematic reviews

Wong and Wilens aimed to include studies recruiting children and adolescents, aged 18 years or younger, and analyzed data from 795 patients with one of the five conditions: seizure, chemotherapy-induced nausea and vomiting (CINV), spasticity, tics, and posttraumatic stress disorder (PTSD).[1]

RCTs

Libzon et al. included 25 patients with complex motor disorder that could be defined as neurologic disorder with a combination of various types of abnormal movements.[2] Cerebral palsy was considered the most common cause of complex motor disorder.[2]

Interventions and Comparators

Systematic reviews

Wong and Wilens aimed to include studies evaluating cannabinoids as the intervention and did not specify the comparators of interest.[1] The interventions identified in the primary studies were cannabidiol, oral cannabis extract, cannabidiol-enriched oral cannabis extract, and Dronabinol (synthetical cannabinoid).[1] The comparators were not reported in all primary studies.[1] The five non-comparative studies included in a CADTH Summary of Abstracts report[7] were included in this SR.

RCTs

Libzon et al. used 5% oil formulation of the cannabis strain Avidekel.[2] The ratios of cannabidiol to tetrahydrocannabinol (THC) were 20:1 and 6:1 in two groups and the concentrations of the two cannabinoids were 5% in total in the oil.[2] The oil was delivered orally and doses were increased until one of the four following conditions were met:

intolerance, serious side effects, maximum THC dose of 15 mg per day, or the end of the study.[2]

Outcomes

Systematic reviews

Wong and Wilens did not set up eligibility criteria for the outcomes in the primary studies.[1] The outcomes assessed in the primary studies were seizure frequency and duration, electroencephalogram (no other details provided), Liverpool Adverse Events Profile, Pediatric Epilepsy Side Effects Questionnaire for epilepsy (for seizure patients), Screen for Child Anxiety Related Disorders, Sleep Disturbance Scale for Children for PTSD, pain intensity (for patients with neuropathic pain), Yale Global Tic Severity Scale, Gilles de la Tourette Syndrome–Quality of Life Scale (for patients with Tourette Syndrome), and adverse events.[1]

RCTs

Libzon et al. assessed spasticity and dystonia, sleep difficulties (measures not reported), pain severity (visual analogue scale), quality of life, and adverse effects using measurement tools, such as the Berry Albright Dystonia scale and the Gross Motor Function Measure.[2] The outcome measures were compared with baseline statistics.[2] There were no direct comparisons between the two groups.[2]

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Summary of Critical Appraisal

Systematic reviews

The clarity of reporting was central to assess the SR. In the SR by Wong and Wilens, the population, intervention, comparator, and outcome components and selection of study design were described in the research questions.[1] The included studies were described.[1] It was reported that there was no funding for the review.[1]

However, the review protocol was not published *a priori*.[1] It was uncertain whether the literature search or review implementation deviated from the original protocol for other purposes that might have introduced biases, such as adding studies without appropriate comparators. Detailed documentation could help to reduce human error. However, excluded studies were not listed.[1] Although the risk of bias in the primary studies seemed to be appraised, the tool to assess the risk of bias was not reported.[1] The comparators were described in some primary studies and the funding sources for the primary studies were not reported.[1]

Human errors in identification of relevant evidence could be minimized via several approaches. A comprehensive literature search was conducted in several databases and the risk of omitting important references was likely minimized.[1] However, study selection and data extraction were not conducted in duplicate.[1]

There were issues that could impact the quality of evidence synthesis, such as risk of bias in and heterogeneity between the primary studies. The risk of bias in primary studies and between-study heterogeneity were considered while interpreting the results.[1]

RCTs

The primary study was first assessed based on the quality of reporting. Libzon et al. described the research hypotheses, study objectives, main outcomes, patient characteristics, interventions, distributions of principal confounders, main findings, and patients lost to follow-up.[2] The random variability in the outcome data was reported.[2] The adverse events were reported.[2] The actual probability values (*P* values) were reported.[2]

The items addressing internal validity of the primary study were assessed. The staff, place, and facilities where the study participants received care were not different from those where the majority of patients received care.[2] The time periods between intervention and outcome were the same for the patients in two groups.[2] The statistical tests used to assess the outcomes were appropriate.[2] Some of the outcome measures were reliable (validated questionnaires were used).[2] However, the patients and the outcome assessors were not blinded.[2] The compliance with the intervention was not reported.[2] The risk of reporting bias might be increased as a result. There was no power analysis for sample sizes in this pilot study.[2] It was uncertain whether this study was under- or over-powered to identify the significance of the outcomes.

Confounding is an important consideration while assessing the primary studies. The patients in two groups were recruited at the same time and the same medical centre.[2] The patients were randomly assigned with the interventions.[2] The risk of selection bias was likely minimized. However, the interventions were not concealed from the patients or the staff.[2] Therefore, the quality of outcome reporting might not be optimal. The patients lost to follow-up were not considered in the analysis and the impact on results was unclear.[2]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Medicinal Cannabinoids

Epilepsy

In the SR by Wong and Wilens, due to heterogeneity between primary studies the findings were not numerically synthesized.[1] Cannabidiol of various dosing strategies was associated with a reduction in seizure frequency in six primary studies and statistical significance was confirmed in one study.[1] Oral cannabis extracts or cannabidiol-enriched oral cannabis extracts were associated with a reduction in seizure frequency in five primary studies, but statistical significance was not mentioned.[1] The follow-up durations in the primary studies were not reported.[1]

Spasticity

In a RCT, Libzon et al. observed significant improvement from baseline in spasticity in 25 patients with severe complex motor disorder receiving 5% oil formulation of cannabis (cannabidiol to THC ratios: 20:1 and 6:1) five months after interventions.[2] This improvement was not significant in the group of patients who received the cannabidiol to THC 6:1 ratio (n = 14). The comparative effectiveness between the two treatment groups was not tested.[2]

Sleep difficulties

In a RCT, Libzon et al. observed significant improvement in sleep difficulties (measures not reported) from baseline in 25 patients using two types of 5% oil formulation of cannabis

(cannabidiol to THC ratios: 20:1 and 6:1) with severe complex motor disorder. This improvement was not significant in the group of patients who received the cannabidiol to THC 20:1 ratio (n = 11).[2]

Pain

In a RCT, Libzon et al. observed significant improvement in pain (visual analogue scale, ranges not provided) in 25 patients using 5% oil formulation of cannabis (cannabidiol to THC ratios: 20:1 and 6:1) with severe complex motor disorder. Improvements were not statistically significant in either treatment group when analyzed separately.[2]

Quality of life

In a RCT, Libzon et al. observed significant improvement in quality of life (Cerebral Palsy Child questionnaire for quality of life, details not provided) in 25 patients with severe complex motor disorder using 5% oil formulation of cannabis (cannabidiol to THC ratios: 20:1 and 6:1). These improvements were also statistically significant when each treatment group was analyzed separately.[2]

Adverse events

In an RCT by Libzon et al., adverse events were considered rare in both groups of patients (25 patients in total) with severe complex motor disorder receiving 5% oil formulation of cannabis (cannabidiol to THC ratios: 20:1 and 6:1). The adverse events that occurred in both groups included sustained increase in creatinine phosphokinase (three patients and behavioural changes (two patients; one controlled by discontinuing methylphenidate, a concurrent medication). Worsening of aminotransferase levels was not observed in any patient.[2]

Clinical Effectiveness of Synthetical Cannabinoids

Epilepsy

In the SR by Wong and Wilens, Dronabinol reduced seizure frequency in two of the six patients in a case series and statistical significance was not reported.[1]

Spasticity

In the SR by Wong and Wilens, Dronabinol was associated with a reduction in spasticity and there was no habituation observed during 181 days of intervention (12 patients in one primary study).[1] Statistical significance was not reported.[1]

Guidelines

No evidence-based guidelines regarding the medicinal and synthetical cannabinoids for pediatric patients were identified; therefore, no summary can be provided.

Appendix 4 presents a table of the main study findings and authors' conclusions.

Limitations

There were no evidence-based guidelines identified for the use of cannabinoids in children. PTSD was the only mental health condition identified in the SR.[1] Epilepsy and spasticity were the sole identified conditions related to neurodegenerative diseases.[1] Neuropathic pain was the only pain disorder studied in one primary study in the SR.[1] There were a limited number of patients included or used for analysis in the identified studies.[1,2] In the SR, the maximal sample size in the primary studies was 137 and nine primary studies

recruited fewer than 10 patients.[1] In addition, six of the studies included in the SR were case series or case reports, which have a descriptive study design that does not provide strong evidence of clinical effectiveness. Although the evidence was supportive for the use of medicinal or synthetical cannabinoids in the SR,[1,2] publication bias was not assessed.[1] In the SR, the dosages of cannabinoids were not uniform.[1] For example, the target dosage of cannabidiol varied between 15 and 20 mg/kg daily in the primary studies if reported.[1] In the SR by Wong and Wilens, the dosages of oral cannabis extracts were not reported in all primary studies.[1] The patients were not selected using the same eligibility criteria or based on standardized diagnostic codes.[1,2] The comparability of the included studies was unclear. Moreover, the synthetical cannabinoid used in the SR by Wong and Wilens, Dronabinol, was not available in Canada.[3]

Conclusions and Implications for Decision or Policy Making

One SR without independent literature selection and data extraction and one fair-quality RCT were identified.[1,2] In the SR, medicinal cannabinoids (particularly cannabidiol and THC) and oral cannabis extracts of various dosing strategies, were associated with a reduction in epilepsy frequency; however, the statistical significance was reported in only one of the 11 primary studies.[1] In the RCT, 5% oil formulations of cannabis with two cannabidiol to THC ratios (6:1 and 20:1) were significantly associated with a reduction in spasticity, sleep difficulties, and pain and an improvement in quality of life relative to baseline in 25 patients with severe complex motor disorder. These effects were not always statistically significant when each treatment group was analyzed separately, and comparative effectiveness between groups was not evaluated.[2] Adverse events occurred in three or fewer of the 25 patients using the oil formulation and were considered rare by the trial authors.[2]

Dronabinol was a synthetical cannabinoid identified in the primary studies in the SR.[1] Dronabinol was associated with a reduction in seizure frequency among epilepsy patients and a reduction in spasticity in patients with spasticity in one primary study.[1]

No evidence-based guidelines were identified, and no summary could be provided.

The limitations to this report were related to small sample sizes in the primary studies, lack of publication bias assessment, and the lack of comparability between primary studies due to the differences in the patients and the types and dosages of cannabinoids.[1,2] Moreover, the synthetical cannabinoid, Dronabinol, is not available in Canada.[3] The identified evidence for this report focused on the following conditions: PTSD for mental health conditions, epilepsy and spasticity for neurodegenerative diseases, and neuropathic pain for pain disorders; no evidence related to other types of mental health conditions, pain, or neurogenerative diseases were identified.[1]

Due to the limited amount of comparative evidence and lack of guidance identified for the use of the cannabinoids in general and for those available in Canada specifically, the clinical effectiveness of medicinal or synthetical cannabinoids in children remains unclear. Further research in the effectiveness of medicinal or synthetical cannabinoids in Canadian contexts may help to reduce uncertainty.

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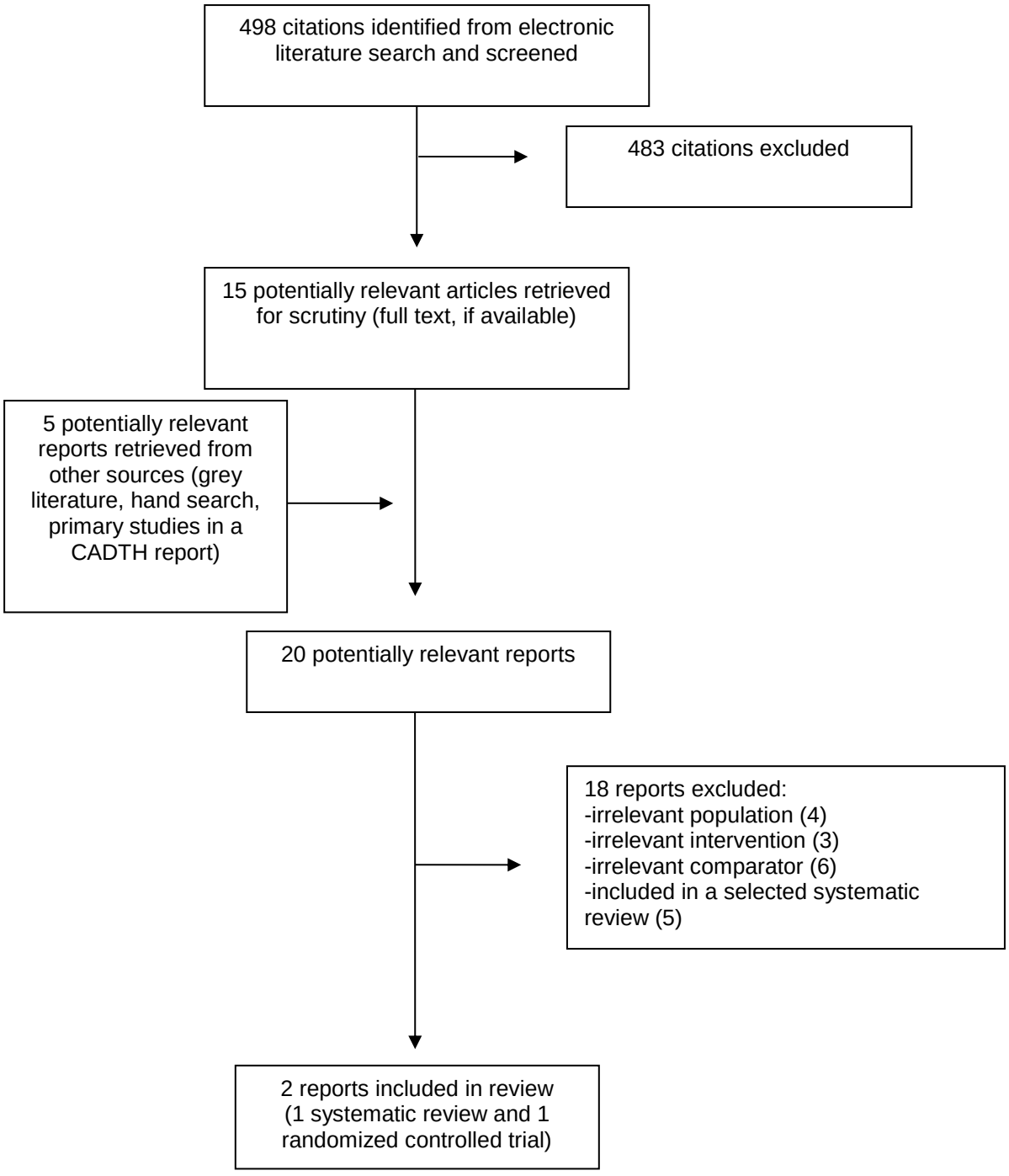
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wong and Wilens 2017,[1] USA	21 studies identified (5 RCTs, 5 retrospective chart reviews, 5 case reports, 4 open-label trials, 2 parent surveys, and 1 case series) Relevant studies for this report: 12 (epilepsy as outcome: 11 studies, spasticity: 1 study) Inclusion criteria: Primary studies with original data eligible English articles eligible Multiple databases searched in May 2017	795 patients 5 conditions [seizure (11 studies), chemotherapy-induced nausea and vomiting (6 studies), spasticity (2 studies), tics (1 study), and PTSD 1 study)] Inclusion criteria: children and adolescents (aged 18 years or younger) eligible	Cannabidiol, oral cannabis extract, cannabidiol -enriched oral cannabis extract, and Dronabinol (synthetical) versus placebo, no comparator (if reported) for epilepsy Dronabinol (synthetic), no comparator (if reported) for neuropathic pain, spasticity, Tourette syndrome Cannabidiol versus no comparator (if reported) for PTSD Inclusion criteria: all cannabinoids eligible; no restrictions on comparators	Outcomes identified Chemotherapy-induced nausea and vomiting: nausea, vomiting Epilepsy: Convulsive-seizure frequency, seizure frequency and duration, electroencephalogram, number of seizures, Liverpool Adverse Events Profile, Pediatric Epilepsy Side Effects Questionnaire for epilepsy Neuropathic pain: 0 to 100 numerical rating scale for pain PTSD: Screen for Child Anxiety Related Disorders, Sleep Disturbance Scale for Children for PTSD Spasticity: spasticity, myoclonus for spasticity Tourette Syndrome: Yale Global Tic Severity Scale, Gilles de la Tourette Syndrome–Quality of Life Scale, Conners' Teacher Rating Scale–Revised: Long for Tourette syndrome Follow-up duration: not reported Inclusion criteria: outcomes of interest not reported

PTSD = posttraumatic stress disorder; RCT = randomized controlled trial.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Libzon et al. 2018,[2] Israel	RCT, single centre, no blinding	Inclusion criteria: aged 1 to 18 years; complex motor disorder with predominant dystonia, spasticity, or both; normal electrocardiogram; and a stable medical condition (no cardiorespiratory and renal deterioration) 25 patients with complex motor disorder (neurologic disorder with a combination of various types of abnormal movements; cerebral palsy the most common) Aged 1 to 17 years Mean age: 6.51 years 16 males and 9 females	Medical cannabis products compared with each other [cannabidiol-enriched 5% oil formulation of the cannabis strain Avidekel (Tikun Olam Ltd)]: cannabidiol to δ-9 - tetrahydrocannabinol (THC) ratios 20:1 (minimal amount of THC) versus 6:1 (higher amount of THC) Route: oral Doses: up-titrated until intolerance, serious side effects, maximum THC dose of 15 mg per day, or the end of the study	Berry Albright Dystonia scale, Gross Motor Function Measure, parents' numeric rating scale for spasticity, dystonia, estimation of mood, sleep (measures not reported), appetite, and constipation, visual analog scale for pain, Cerebral Palsy Child questionnaire (chapter 6, for quality of life), and questionnaires for adverse effects, electrocardiogram, electroencephalogram, and blood tests, adverse effects Follow-up: 5 months

RCT = randomized controlled trial; THC = tetrahydrocannabinol.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[13]

Strengths	Limitations
Wong and Wilens, 2017[1]	
- PICO components mentioned in the research questions - Selection of study design explained - Comprehensive literature search - Included studies described - Risk of bias in the included studies considered while discussing the results - Funding sources for the review reported	- Review protocol not published *a priori* - Study selection not in duplicate - Data extraction not in duplicate - Excluded studies not listed - Unknown tools to assess the risk of bias in the included studies - Funding sources for the included studies not reported

AMSTAR = A Measurement Tool to Assess Systematic Reviews; PICO = population, intervention, comparator, and outcome.

Table 5: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[14]

Strengths	Limitations
Libzon et al., 2018[2]	
- Hypotheses and study objectives described - Outcomes to be measured described - Patient characteristics reported - Interventions of interest described - Distributions of principal confounders in two groups compared - Main findings described - Estimates of random variability in the outcome data provided - Adverse events reported - Patients lost to follow-up reported - Actual probability values (*P* values) reported - The staff, place, and facilities where the enrolled patients received the care not different from those where the majority of patients received care - The time periods between intervention and outcome the same for the two groups - Appropriate statistical methods to assess the main outcomes - Outcomes measured accurately - Patients in two groups recruited at the same time and from the same source - Patients randomized into two groups	- Patients and outcome assessors not blinded - Compliance with the medication not reported - Assigned interventions not concealed - Patients lost to follow-up not considered in the analysis - No power analysis for sample sizes in this pilot study

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Wong and Wilens, 2017[1]	
Medical Cannabinoids for Chemotherapy-induced Nausea and Vomiting (6 studies) - Not eligible for this report Medical Cannabinoids for Epilepsy (11 studies) - Devinsky 2017: "*CBD significantly reduced convulsive seizure frequency in children with treatment-resistant epilepsy in Dravet syndrome as compared with a placebo*" (p. 6) - Devinsky 2016: "*CBD reduced seizure frequency in a pediatric population with childhood-onset treatment-resistant epilepsies from a range of different causes*" (p. 6) - Kaplan 2017: seizures reduced in 3 of the 5 patients "*in a small open-label case series of CBD for patients with treatment-refractory epilepsy in Sturge-Weber syndrome*" (p. 6) - Gofshteyn 2017: seizures reduced in 6 of the 7 patients "*in a similar open-label case series of CBD for patients diagnosed with febrile infection-related epilepsy syndrome*" (p. 6) - Treat 2017: "*in a retrospective chart review of 119 pediatric patients with epilepsy, …oral cannabis extracts improved seizures in 49% of the cohort, with 24% of the patients considered responders as defined by a >50% reduction in seizure burden*" (p. 6) - Press 2015: "*in a second retrospective chart review from the same institution, … oral cannabis extracts reduced seizures in 57% of the 75 patients with treatment-refractory seizures*" (p. 6) - Tzadok 2016: "*CBD-enriched medical cannabis reduced seizures in 89% of patients*" in a retrospective chart review of 74 children and adolescents with treatment-resistant epilepsy (p. 6) - Porter and Jacobson 2013: "*In a small survey of 19 parents of children with treatment-resistant epilepsy, … CBD-enriched cannabis reduced seizure frequency in 84% of patients*" (p. 6) - Hussain 2015: "*CBD-enriched cannabis reduced seizures in 85% of*" (p. 7) 117 parents of children with epilepsy - Lorenz 2004 (Dronabinol, synthetical cannabis): "*In a case series of 6 children with epilepsy, … dronabinol reduced seizures in 2 of the patients*" (p. 7) - Saade and Joshi 2015: "*CBD reduced seizure frequency in a 10-month-old patient with malignant migrating partial seizures of infancy*" (p. 7) Medical Cannabinoids for Spasticity (1 study) - Kuhlen 2016 (Dronabinol, synthetical cannabis): "*Dronabinol solution given twice daily reduced spasticity and was continued for a median of 181 days with no habituation observed*" (p. 7) at a palliative care setting Medical Cannabinoids for Other Indications (2 studies) - Not eligible for this report	- "*Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting, with increasing evidence of benefit for epilepsy. At this time, there is insufficient evidence to support use for spasticity, neuropathic pain, posttraumatic stress disorder, and Tourette syndrome*" (p. 1) - "*Additional research is needed to evaluate the potential role of medical cannabinoids in children and adolescents, especially given increasing accessibility from state legalization and potential psychiatric and neurocognitive adverse effects identified from studies of recreational cannabis use*" (p. 1)

CBD = cannabidiol.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized controlled trials	
Libzon et al., 2018[2]	
Change from baseline in each outcome with 5% oil formulation of cannabis at cannabidiol to THC ratios: 20:1 (n = 11) and 6:1 (n = 14), (mean ± standard deviation) **Spasticity and dystonia (Barry Albright Dystonia Scale):** All patients (n = 25): 15.68 ± 6.25 to 12.69 ± 4.62 (*P* = 0.009) 20:1 group: 17.00 ± 3.87 to 13.55 ± 3.56 (*P* = 0.021) 6:1 group: 14.64 ± 7.58 to 11.97 ± 5.39 (*P* = 0.951) (5-month follow-up) **Sleep difficulties (numeric rating scale, not otherwise described):** All patients (n = 25): 3.48 ± 2.00 to 5.08 ± 1.19 (*P* = 0.002) 20:1 group: 3.55 ± 2.25 to 4.73 ± 1.62 (*P* = 0.107) 6:1 group: 3.43 ± 1.87 to 5.36 ± 0.63 (*P* = 0.011) **Pain severity (visual analogue scale):** All patients (n = 25): 5.68 ± 3.14 to 4.27 ± 2.65 (*P* = 0.022) 20:1 group: 4.91 ± 3.49 to 3.62 ± 2.67 (*P* = 1) 6:1 group: 6.22 ± 2.87 to 4.74 ± 2.63 (*P* = 0.426) **QOL:** All patients (n = 25): 40 (0-80) to 60 (20-80) (*P* = 0.036) 20:1 group: 30.91 ± 20.71 to 57.78 ± 12.02 (*P* = 0.023) 6:1 group: 46.67 ± 21.46 to 55.38 ± 20.56 (*P* = 0.011) **Adverse events:** behavioural change in 2 patients (one controlled by discontinuing methylphenidate), sustained increase in creatinine phosphokinase in three patients, no worsening in aminotransferase levels	- No between-group comparisons - "*Significant improvement in spasticity and dystonia, sleep difficulties, pain severity, and QOL was observed in the total study cohort, regardless of treatment assignment. Adverse effects were rare and included worsening of seizures in 2 patients, behavioral changes in 2 and somnolence in 1*" (p. 565)

QOL = quality of life; THC = tetrahydrocannabinol.

Appendix 5: Additional References of Potential Interest

Reviews without systematic literature searches

Artukoglu BB, Bloch MH. The Potential of Cannabinoid-Based Treatments in Tourette Syndrome. *CNS Drugs.* 2019;33(5):417-430.

Billakota S, Devinsky O, Marsh E. Cannabinoid therapy in epilepsy. *Curr Opin Neurol.* 2019;32(2):220-226.

Chye Y, Christensen E, Yucel M. Cannabis Use in Adolescence: A Review of Neuroimaging Findings. *J Dual Diagn.* 2019:1-23.

Krebs MO, Kebir O, Jay TM. Exposure to cannabinoids can lead to persistent cognitive and psychiatric disorders. *Eur J Pain.* 2019;23(7):1225-1233.

Patel J, Marwaha R. Cannabis Use Disorder. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2019: https://www.ncbi.nlm.nih.gov/books/NBK538131/

Perry MS. Don't Fear the Reefer-Evidence Mounts for Plant-Based Cannabidiol as Treatment for Epilepsy. *Epilepsy Curr.* 2019;19(2):93-95.

Rod Rassekh S. Urgent need for "EBMM" in pediatric oncology: Evidence based medical marijuana. *Pediatr Hematol Oncol.* 2019;36(5):253-254.

Treister-Goltzman Y, Freud T, Press Y, Peleg R. Trends in Publications on Medical Cannabis from the Year 2000. *Popul Health Manag.* 2019;22(4):362-368.

Corroon J, Kight R. Regulatory Status of Cannabidiol in the United States: A Perspective. *Cannabis Cannabinoid Res.* 2018;3(1):190-194

Guidelines without systematic literature searches

Mack DR, Benchimol EI, Critch J, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Medical Management of Pediatric Luminal Crohn's Disease. *Gastroenterology.* 2019;157(2):320-348.