# Abstract

**Background:** Drug-resistant epilepsy among children remains a common neurological disorder that imparts a burden to families, patients, and the broader healthcare sector. Research suggests the capacity of cannabidiol to treat intractable epilepsy among children.

**Purpose:** The current systematic review aims at exploring the evidence on the efficacy of cannabidiol (CBD) interventions in treating childhood intractable epilepsy.

**Method:** Systematic review of clinical trials, randomised controlled studies, and medical research exploring the application of cannabidiol in the treatment of intractable epilepsy. Studies using cannabidiol intervention in drug-resistant epileptic children with a mean age of 18 years and below were included within the systematic review process.

**Results:** Eight primary studies were included within the systematic review published 2013 and later (N=8). Findings indicate significant evidence on the influence of cannabidiol intervention in reducing seizure activity by more than 50% among children with intractable epilepsy. Further, positive outcomes of CBD were established on the general quality of life, including sleep outcomes, increased alertness, and improved moods. However, results indicate significant adverse side effects of CBD therapy.

**Discussion:** The capacity of cannabinoids to influence the inhibition and function of neurotransmitters plays an integral role in the treatment of childhood intractable epilepsy. Through influencing the inhibition dynamics of neurotransmitters, CBD imparts its anticonvulsant and anxiety properties which significantly reduces the frequency of seizures and severity of seizure activity on affected children.

**Conclusion:** The mechanism of action encompassed within CBD based treatment influences the seizure activity through influencing neurological transmission. The application of CBD treatments significantly reduces the frequency of seizures and improves general seizure control among children with intractable epilepsy. Further, cannabidiol holds additional health benefits that improve the patient's quality of life.

**Keywords:** *Intractable epilepsy, Seizure frequency, Cannabidiol (CBD), Neurological transmission*

# Introduction

Following the significantly high prevalence of epilepsy among children within the present society, effective therapies and treatment are important for improving neurologic conditions among the affected children. The elongated subjection of infants and children to epileptic convulsions significantly affects the healthy growth, life quality and development of life. Multiple therapies are adopted within conventional medical practices for treatment and care for children with epilepsy. However, children affected with intractable epilepsy experience limited positive outcomes from conventional pharmacological and medical treatments.

The systematic review of evidence on applicability of CBD enriched therapies for the treatment of intractable epilepsy generates resourceful information that appraises the contemporary medical and research practice regarding epilepsy. Through systematic testing of the hypothesis that cannabidiol influences the healing process in the medical treatment of epilepsy, the current systematic review improves the contemporary understanding of epileptic seizures and health outcomes among children with intractable epilepsy. The lack of a precise treatment approach within medical practice attributes to the application polytherapy for treating epilepsy. Drawbacks on the contemporary medical polytherapy include; increased risk of sudden unexplained death in epilepsy patients (SUDEP), depression, fatigue, and memory issues which emerge from the pharmacodynamic dose-based neurotoxic impacts from polytherapy (O'Connell et al., 2017). While the conventional pharmacological treatments impart insignificant positive outcomes on treating drug-resistant epilepsy, there is a need for contemporary medicine and healthcare to establish improved treatments that can alleviate the negative health effect of the neurological disorder.

## *Background Information*

Epilepsy is a neurological disorder that affects individuals of all ethnic backgrounds, ages, and races where the central nervous system (CNS) reflects abnormal behaviour, sensations, and reduced levels of consciousness (Devinsky et al., 2017). A seizure is characterised by the rapid and uncontrolled electrical disturbance within the central nervous system due to abnormal discharge of cortical neurons leading to sudden changes in movements and general behaviour (Rosenberg et al.,2015). Epileptogenesis emanates from the changes in electrical structure and balance within the neurological transmission systems which attributes to the development of recurrent seizures. The high hypersynchronous electrical discharge of neurons within the CNS affects the balance between neurological excitation and the brain inhibition, which results in a significant excitatory overload. The excitatory-inhibitory imbalance within the brain's neurological structure attributes to the development of seizures, which can recur, often leading to epileptic neurological disorder (Rosenberg et al., 2015).

During epileptic seizures, affected individuals undergo rapid changes in body sensations, normal behaviour, and general awareness of their environments. The evolving research and interests in the applicability of cannabis within medical research and clinical settings are based on the capacity of cannabinoids to influence the treatment of various disorders. While multiple therapeutic effects on the physical and psychological health domains reflect the medicinal value of marijuana, physicians and medical practitioners have recommended and practised alternative healing perspectives through using marijuana. The normal usage of marijuana remains under legal, ethical, and social controversies where restrictions are imposed by drug enforcement and drug abuse agencies (O'Connell et al., 2017).

From a broader perspective, childhood epilepsy manifests as either benign epilepsy or drug-resistant epilepsy. While benign epilepsy affects a large percentage of individuals within the general population, drug-resistant epilepsy poses higher health risks as it encompasses chronic forms of convulsions such as idiopathic and genetic epileptic encephalopathies, as well as acquired epileptic syndromes (Friedman and Devinsky, 2015). The epileptic encephalopathies, Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS) significantly account for one to four per cent of reported childhood epilepsy. Lennox-Gastaut Syndrome (LGS) affects children between the age of 2 and 7, where patients undergo various forms of epileptic seizures myoclonic, tonic and atonic seizures (Devinsky et al., 2017). Dravet syndrome remains characterised by prolonged seizures within the children's first year accompanied by fever and other health issues on the infant.

The World Health Organization (WHO) reports that there has been an annual increase in the consumption of marijuana for both general and medicinal purposes where nearly 2.5% of the global population consumes cannabis and its products. Although the excessive or abusive usage of marijuana holds adverse effects on the user's physical and psychological health domains, ancient cultures, and medical research identify the capacity of medicinal marijuana to treat epileptic convulsions. The World Health Organization (WHO) reports that approximately 50 million individuals across the globe suffer from epilepsy, making it the most prevalent neurological disorder (WHO, 2019). In principle, the marijuana plants, Cannabis sativa, and Cannabis indica encompass approximately 500 distinct chemical substances that contain varying phytocannabinoid compounds (Fig 1). The primary elements within cannabis, Δ-9-tetrahydrocannabinol (THC) and CBD have acquired high medical and clinical interest due to their impacts and putative effects on the prevention of seizures. While Δ-9-tetrahydrocannabinol (THC) imparts psychoactive effects on the users, the equivocal value of THC plays an imperative role in the control of seizure activities as well as triggering seizures. Further, anecdotal and scientific evidence indicates the role of the non-psychoactive agent, CBD, on antiepileptic medication within the contemporary medical settings (Friedman and Devinsky, 2015; O'Connell et al., 2017)



Fig 1: *Molecular structure of THC and CBD*

Biologically, the primary mechanism of THC affects the endogenous cannabinoid receptors CB1 and central nervous system (CNS) receptors within the brain systems. Further, cannabidiol (CBD) positively influences the inhibitory capacity of THC binding to CB1 and CNS receptors thereby facilitating the reduction of anxiety, stress, and paranoia due to CBD's non-modulated activation (Fig 1). Treatment of epileptic convulsions within the conventional medical and clinical settings relies on the anticonvulsant capacities of CBD and THC within the central nervous system. The multifactorial function of CBD influences the gamma-aminobutyric acid (GABA)-mediated inhibition of glutaminergic nerve cells within the CNS (Todd and Arnold, 2016).



Fig 2: *Mechanism of Action of CBD on neurotransmitter targets*

Source: <https://www.mdpi.com/1422-0067/21/3/723/htm>

Cannabidiol highly influences the inhibitory function of the neurotransmitters; GABA, glutamate and CNS receptors (Fig 2). During the binding process of CBD to GABA­A receptor subtypes, CBD proliferates its anticonvulsant and antianxiety properties, thereby appraising the treatment of epilepsy ((Rosenberg et al.,2015). However, CBD does not competitively bind with benzodiazepine receptortargets, which allows for the treatment of epilepsy in individuals resistant to benzodiazepines. The significant influence of CBD on the structure and function of neural activity affects the normal inflammatory components of epileptiform activity thereby providing a means for assessing the manifestations of epilepsy among children and the general population (Ibeas Bih et al., 2015). Further, CBD's affinity for 5-HT2A and 5-HT2A receptors holds an integral role in the refractory treatment of epileptic convolutions within contemporary healthcare environments.

## *Research Objectives*

1. To examine and synthesise the effects of CBD interventions in the treatment of epilepsy among infants and children.
2. To explore the influence of THC and CBD in treating epileptic convulsions among the children.
3. To examine the quality of evidence within medical research and clinical trials on the effectiveness of marijuana in treating epilepsy.

## *Significance of the Systematic Review*

The systematic review of cannabis' influence on the treatment of epilepsy among young children generates resourceful information and an understanding of contemporary evidence for medical and clinical practice. In essence, understanding cannabinoids and their positive therapeutic influence appraise the quality of alternative procedures and treatments which actively adopt medicinal marijuana. Through the systematic review of medical research and clinical trials on medicinal marijuana, the emerging evidence within research reflects the capacity of cannabinoids (CBD) in the treating of epileptic convulsions among children. Further, the review appraises the understanding of medical modifications, treatment procedures, and practices during the application of medicinal marijuana in antiepileptic treatments. Critical evaluation of clinical trials and medical research on medicinal marijuana remains important for guiding decision making and medical practices adopted during the usage of marijuana extracts in treating epilepsy among children. As per the current research's rationale and hypothesis, the application of cannabidiol (CBD) extracts in the treatment of epilepsy have a positive influence on the control of epileptic seizure activity and frequency thereby appraising the health and treatment outcomes of children with intractable epilepsy.

# Materials and Methods

## *Search Strategy*

While current systematic review seeks to answer the primary research problem through the assessment and synthesis of evidence established from both empirical and qualitative studies, an initial search for systematic reviews (SR) was performed on Cochrane and PubMed databases. The results indicated zero SR conducted on the application of cannabinoids for treating epilepsy among children.

Through implementing the review practices and guidelines encapsulated within Cochrane handbook of systematic reviews, the search strategy the consistency and quality of evidence established from the critical assessment of research information (Campbell Collaboration, 2015; Hammerstrøm et al., 2010; Higgins and Green, 2011). The primary databases adopted for the search process include PubMed, Cochrane, the British Medical Journal (BMJ), and Excerpta Medica Database (EMBASE). Further, google scholar and search databases were actively adopted for the data collection process.

The search strategy adopted key search terms throughout various databases for the gathering of studies for review. The primary terms used include "The use of cannabinoids in the treatments of intractable generalised epilepsy in children", "Medical marijuana in epilepsy treatment" "Cannabinoid AND Interactable epilepsy", "Alternative marijuana therapy in epileptic convulsions" "Medical marijuana AND epilepsy treatment".

To effectively develop the search strategy, the initial search applies filters to enable the distinctive search of relevant studies and information from the electronic databases. Individual search terms were initially reviewed in titles and abstracts [Titles/Abstracts] of the search results. In essence, the usage of filters and specific keywords allows for the generation of proximal search results for the data collection process, which significantly appraised the quality of evidence.

## *Inclusion/Exclusion Criteria*

The adopted inclusion criteria collect medical studies and clinical trials that explore the research area while using children as primary participants. For proper classification of individuals during the inclusion process, the systematic review adopts Kail's (2011) classification of children and their development processes. In essence, the categorisation of children depends on the age factor where newborn babies, infants, toddlers, pre-schoolers, school-aged children, and adolescents are classified as children (Kail, 2011). From a broader perspective, all individuals under the age of 19 years are considered eligible for the research. The exclusion criteria exclude medical research, clinical trials, and research exploring epilepsy treatment in adults (Table 1). Through selecting studies which examine cannabidiol effect in treating intractable epilepsy, the review acquires admissible evidence which allows for understanding the quality of evidence on CBD treatments. The criteria adopt patients under the age of 19 years to ensure that the review of the included studies presents evidence on the efficacy of cannabidiol therapies on treating intractable epilepsy among children. Further, studies published before 2000 will be excluded to ensure the review uses recent evidence to achieve the research objectives. Through removing clinical trials and medical research before 2000, the criteria appraise the quality of evidence established from the systematic review of the current research base.

**Table 1:** *Inclusion and Exclusion criteria for eligibility of research papers in the review*

|  |  |
| --- | --- |
| **Include** | **Exclude** |
| Studies and Articles:* Study children mean age <19 years
* Use CBD-based treatments for epileptic children
* Written in English
* Abstracts hold multiple keywords related to the study focus.
 | Studies and Articles:* Studies published before 2000
* Focusing on polytherapy for epilepsy treatment
 |

## *Quality Assessment*

Further, synthesis of evidence adheres to the causal chain, which serves to ensure the current systematic review remain oriented at reporting effects and the underlying reasons for identified effects of the research phenomena. Qualitative evidence is implemented within the data synthesis through the implementation of the effectiveness plus approach (Snilstveit et al., 2012). The effects established from the systematic review of empirical studies are pooled with qualitative evidence for appraising the general quality of evidence on the influence of medicinal marijuana in treating epilepsy in children.

Studies included within the systematic review were actively subjected to quality assessment based on the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies. The adopted quality assessment tool allowed for the examination of evidence-based selection bias, study design, confounding factors, blinding, data collection methods, and withdrawals during the study process. Rating the studies reflects the quality of evidence-based on the primary assessment factors within the EPHPP Quality Assessment Tool.

Three primary ratings are issued for all assessments (1 = strong, 2 = moderate, 3 = weak) (Table 2) (EPHPP, 2009).

Results

Search strategy results provided a total of 291 studies using PubMed and Cochrane, although most were duplicates. On the removal of duplicates from the search results, 102 articles remained. The implementation of the screening process based on the inclusion and exclusion criteria eliminated 189 studies that did not meet the inclusion criteria. In essence, 27 papers were left for full-text examination where 10 papers were excluded as one article explored epilepsy in young adults and the 9 others were past the data collection date set up by the current research. From a broader perspective, 8 studies were actively included within the systematic review of cannabinoids' influence in the treatment of intractable epilepsy among children (Figure 2). All 8 included studies primarily explored the implementation of medicinal marijuana in the treatment and care of acute and drug-resistant epileptic convulsions in children.

**Figure 3:** *PRISMA – flow diagram of the selection process*

Articles and Research identified through Google Search and Scholar Databases

(N=87)

Articles included in the Systematic Review

(N=8)

Papers excluded after full-text assessment

(N=19)

* One was past the set data collection date
* Two studies explored epilepsy treatment in young adults

Papers after removing duplicates

(N=102)

Papers adopted for Full-text examination

(N=27)

Papers Screened

(N=102)

Papers excluded after the Screening process

(N=75)

Articles and Research identified through PubMed and Cochrane

(N=204)

## **Table 2**: *Quality Assessment of Included studies*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and year** | **Selection bias** | **Study design** | **Confounders** | **Blinding** | **Data collection methods** | **Withdrawals and drop-outs** | **Global rating** |
| Hussain (2015) | 2 | 1 | 1 | 1 | 2 | 1 | **1** |
| Devinsky (2014) | 2 | 1 | 1 | 2 | 2 | 1 | **1** |
| Tzadok et al., (2016) | 3 | 1 | 1 | 1 | 2 | 2 | **2** |
| Devinsky et al., (2017) | 2 | 1 | 2 | 2 | 2 | 1 | **1** |
| Kaplan et al., (2017) | 3 | 2 | 1 | 3 | 1 | 2 | **3** |
| Press et al., (2015) | 2 | 2 | 1 | 3 | 2 | 2 | **2** |
| Neubauer et al., (2017) | 2 | 2 | 1 | 3 | 2 | 2 | **2** |
| Porter & Jacobson (2013) | 1 | 2 | 1 | 3 | 2 | 3 | **2** |

## *Efficacy of CBD Treatment of Intractable Epilepsy*

Six studies explored the efficacy of cannabinoids on the treatment of convulsions among individuals, especially children suffering from epileptic seizures. In Israeli, Tzadok et al., (2016) found that medical cannabis oil used for treating intractable epilepsy among children significantly reduces the seizure frequency by 75-100%, 25 children (34%), 50 – 75%, 9 children (12%) 25 – 50% whereas 19 children (26%) reported <25% reduction in seizure frequency (Table 3). Findings from Tzadok et al., (2016) are consistent with Devinsky et al., (2015) establishments on a general median reduction in the occurrence of seizures in 33% of the study population based on the recorded baseline characteristics. Similarly, Devinsky et al. (2015) found that 39% of the study population reported a significant reduction in seizures by up to 50 %. In both studies, the continuous administration of cannabidiol-based treatment (1 to 20mg/kg/day) attributed to the reduction of seizure activity which averaged at 50% seizure activity (Tzadok et al., 2016; Devinsky et al., 2015). In essence, the studies establish the capacity of cannabidiol based extracts and treatments on control and management of seizure activity among patients with drug-resistant epilepsy.

Devinsky et al. (2015) found that four children (17%) became seizure-free after 3 months, where one of the three patents was initially diagnosed with Dravet Syndrome. The researchers revealed that patients entering the study with Dravet Syndrome had a greater than 50% probability of a reduction in seizure activity and 40% general reduction from median baseline characteristics (Table 5). Devinsky et al. (2015) remain consistent with a clinical trial by Neubauer et al., (2018) where 14 patients (21.25) became seizure-free after the clinical procedures. In both Neubauer et al., (2018) and Devinsky et al., (2015), CBD dosages of 8mg/kg/day and ranges of 1 to 20 8mg/kg/day respectively completely alleviated the convulsive seizures in children with intractable epilepsy rendering them seizure-free. In essence, the studies demonstrate the capacity of stale doses of cannabidiol to completely control the convulsions affecting epileptic children.

Another study by Kaplan et al. (2017) found a 50% reduction in seizure activity at week 14 and the last period, respectively (N=5). Further, all the patients reported a significant improvement in their quality of life and therefore continued the use of cannabidiol throughout the 63rd to 80th week. Similarly, press et al., (2015) reported a significant improvement in the control of seizure activity whereas 33% more than 50% reduction in the experiences of seizures as reported by 57% of the responders. In the same manner, findings from Devinsky et al., (2017) established a significant decrease in convulsive seizures per month from 12.4 to 5.9 using cannabidiol treatment as compared to a recorded decrease of 14.9 to 14.1 with placebo (the adjusted median difference between the cannabidiol group and the placebo group in the change in seizure frequency, -22.8 percentage points; 95% confidence interval [CI], -41.1 to -5.4; P=0.01).

Devinsky et al. (2017) support Kaplan et al. (2017), where findings remain consistent on the influence of cannabidiol treatment to reduce seizure frequency by 50% or more. Devinsky et al. (2017) support findings from Hussaini et al. (2015) and Porter and Jacobson (2013) as patients were identified to report the total treatment of the seizures rendering the children seizure-free. The effective administration of cannabidiol based treatment was established to highly reduce the frequency of epileptic seizures among children with drug-resistant epilepsy and severity of seizure activities (Hussaini et al., 2015; Kaplan et al., 2017; Porter and Jacobson, 2013). However, although the overall frequency of seizures was reduced using cannabidiol treatment (p=0.003), Devinsky et al., (2017) found that there was no significant influence of CBD treatment in the reduction of non-convulsive seizures. Throughout the review of the studies, evidence indicates the high capacity of cannabidiol mechanism and properties to suppress the seizure activity, thereby significantly reducing the frequency of seizures among children with intractable epilepsy. The effective administration of CBD enriched therapies imparts positive healing outcomes on the patients.

Evidence from the six studies demonstrates the efficacy of cannabidiol based treatment on reducing the frequency of seizure among children with intractable epilepsy where patients reported reduction by 25%, 50% and up to 75% seizure alleviation. In essence, the studies provide class III evidence that CBD therapies which include add on, oral cannabidiol extracts (OCE) and other cannabidiol based treatments, positively influence the patient's control and management of seizure activity (Press et al., 2015; Devinsky et al., 2015; Devinsky 2017; Kaplan et al., 2017; Neubauer et al., 2018; Tzadok et al., 2016). Across the reviewed studies, the continuous and effective administration of CBD based treatment reflected efficacy in treating the convulsive characteristics of intractable epilepsy, where some patients became seizure-free. Although the six studies report positive CBD treatment outcomes on the reduction of seizure activity, the CBD administration did not affect 15 patients (22.7%) (Table 6) (Neubauer et al., 2018). Conversely, Kaplan et al., (2017) found poor outcomes arising from the usage of cannabidiol to treat the epileptic conditions in patients with Sturge-Weber syndrome brain conditions and intractable epilepsy (Table 7). From a broader perspective, the clinical trial advocates for the application of cannabidiol (CBD) as an adjunctive medication for the management of seizures.

## *Perceived Efficacy of Cannabidiol Enriched Treatments*

An open-label trial by Hussaini et al., (2015) found that the administration of CBD treatment to refractory patients for 6.8 months and 4.3mg/kg/day attributed to a significant reduction in seizure frequency whereas 14% reported seizure-free children after using the CBD treatment (Table 11). Findings from Hussaini et al. (2015) support the findings of Porter and Jacobson (2013), where 2 parents (11%) reported the total treatment of the seizures rendering their children seizure-free. Eight parents (42%) indicated a higher reduction in seizure activity up to 80% while six (32%) reported a 25-60% reduction in the frequency of convulsions (Table 10). Evidence from the studies reveals the high perceived efficacy of cannabidiol treatment in the neurological control and management of the patient's seizure activity, thereby reducing the adverse effects of epileptic convulsions. In essence, the usage of cannabidiol therapies significantly appraises the healing outcomes of epilepsy patients as reported by parents and guardians. Fundamentally, CBD treatments highly target the inhibitory mechanisms causing seizures, thereby attributing to the reduction of seizures up to 50%.

## *Health Benefits of CBD Treatments*

Research acknowledges the accompanying positive outcomes during CBD treatments among epileptic patients. Tzadok et al. (2016) reported improved outcomes in children's behaviour and alertness, general motor skills, communication capacity, and sleep. Negative reactions from the CBD treatment procedure included fatigue, somnolence, irritation, and discomfort, which attributed to the withdrawal of 5 children from the research process. Further, a high percentage of the respondents reported significant improvements in sleep outcomes (53%), level of alertness (71%), and mood (63%) after usage of the CBD therapy (Hussaini et al., 2015). In agreement with Tzadok et al., (2016) and Hussaini et al., 2015, Porter and Jacobson (2013) established additional benefits from the application of CBD therapy include higher alertness, improved sleep outcomes, and healthy moods. Similarly, Press et al., (2015) established positive outcomes from the system-wide implementation of OCE for epilepsy treatment include; improved motor capacities (10%), higher alert behaviour (33%), and improved language (10%).

## *Adverse Effects of Cannabidiol Intervention*

Five studies record the significant negative outcomes associated with cannabidiol based treatments. Primary adverse reactions include somnolence (57%), fatigue (57%), decreased appetite (22%), diarrhoea (22%), and weight loss (9%). Following the severity of some reactions on the children included within the research process, the accumulated dosages were reduced from 25 mg/kg/day to 20 mg/kg/day, which significantly improved the outcomes and symptoms of side effects (Devinsky et al., 2015). During the research by Tzadok et al., (2016), 5 children (7%) reported the significant aggravation of epileptic seizures which warranted the withdrawal of CBD treatment. In Press et al., (2015), 44% of the patients experienced adverse events (AEs) within the clinical settings where the events include seizures (13%) and somnolence/fatigue (12%). Adverse events reported within Devinsky et al., (2017) the CBD group as compared to the placebo group include fatigue, vomiting, discomfort, and liver disorientation. Hussaini et al., (2015), reported side effects from the exposure to CBD treatment included an increase in appetite in 30% of the study population.

## **Table 3.** *Summary of Study Characteristics of Included Studies*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author and year** | **Population****(P)** | **Interventions****(I)** | **Comparison****(C)** | **Outcome measures****(O)**  | **Study design****(S)** |
| Hussain (2015) | Canada | CBD treatment to refractory patients was 6.8 months and 4.3mg/kg/dayInfantile spasms (IS) and Lennox-Gastaut syndrome (LGS) | No control | Reduction in seizure frequency (85%)Seizure free children (14%) | Parent Survey |
| Devinsky (2015) | United Status | Cannabidiol treatment daily dosage was increased by 5 mg/kg/day to a 25 mg/kg/day dosage limitAverage dosage: 20 mg/kg/day | Control Group | The median reduction in the occurrence of seizures (33%) Seizure free (17%) | A randomized controlled trial with a five-year follow-up |
| Tzadok et al. (2016) | Sweden | Medical cannabis oil encapsulating CBD and tetrahydrocannabinol ratio of 20:1 where the administered doses ranged from 1 to 20mg/kg/d. | Control group | Reduction of seizure frequency by 75-100% (18%), 50 – 75% (34%), <25% reduction (26%)  | Retrospective cohort study |
| Devinsky et al., (2017) | United States | CBD dose of 20 mg per kilogram of body weight per day | A double-blind, placebo-controlled trial | 50% reduction in the frequency of epileptic seizures (43%) | Randomized control trial (RCT) |
| Kaplan et al. (2017) | Sweden | Cannabidiol medical treatment | Placebo-controlled | 50% reduction in seizure activity at week 14 | clinical trial designMouse model of Dravet Syndrome |
| Press et al. (2015) | Denmark | CBD enriched pharmacological treatments | Placebo-controlled | Control of seizure activity (57%)Reduction in the experiences of seizures (>50%)Dravet 23%, Doose, and Lennox-Gastaut syndrome (LGS) 88.9%. | Retrospective Chart Review |
| Neubauer et al. (2017) | Slovenia | CBD treatment dosage at least 8mg/kg/day 50% improvement in seizure frequency, whereas 14 patients (21.25%) became seizure-free after the clinical procedures. | Control group | 50% improvement in seizure frequency, whereas 14 patients (21.25%) became seizure-free after the clinical procedures. | Prospective cohort |
| Porter & Jacobson (2013) | United States | Cannabidiol based treatments  | No control | Reduction in the occurrence of seizures (84%) | Parent Survey |

## **Table 4.** *Studies Investigating Efficacy of CBD Treatment of Intractable Epilepsy*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Subjection to CBD treatment Interventions** | **Outcome measures** | **Results**  |
| Tzadok et al. (2016) Retrospective cohort study | To investigate the clinical experiences of five paediatric epilepsy clinics treating children in Israeli using CBD interventions | The cohort study included 74 patients (age range 1-18 years) who had been identified with intractable epilepsy resistant to more than 7 epileptic pharmacological drugs | Medical cannabis oil was adopted for treatment having a CBD and tetrahydrocannabinol ratio of 20:1 where the administered doses ranged from 1 to 20mg/kg/d | Patients reported seizure frequency and severity of seizure activity. | Epilepsy Treatment OutcomesIncreased self-reporting from affected children on the reduction of seizure frequency (66/74, 89%). Further, 13 children (18%) reported the reduction of seizure frequency by 75-100%, 25 children (34%) reported 50 – 75%, 9 children (12%) reported seizure reduction between 25 – 50% whereas 19 children (26%) reported <25% reduction in seizure frequency.Allergic outcomes in ChildrenFive children (7%) reported the significant aggravation of epileptic seizures which warranted the withdrawal of CBD treatment.  |
|  |

## **Table 5:** *Studies Investigating the Efficacy of CBD Treatment of Intractable Epilepsy*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Subjection to CBD treatment Interventions** | **Outcome measures** | **Results**  |
| Devinsky et al. (2015) Clinical Trial | To investigate CBD efficacy and effectiveness in the treatment of children with intractable epilepsy (Mean age of 10.4 years). | The clinical trial included 23 patients, 9 patients (39%) were diagnosed with Dravet Syndrome, 4 patients (17%) had Myoclonic-Absence Epilepsy, 3 (15%) had Lennox Gastaut whereas the rest had generalized epilepsies. Baseline data on the study participants were recorded through a 4-week baseline period where all seizure activity regarding the patients was recorded.  | Patients were subjected to oil-based extract encompassing 98% CBD administered at the dosage rate of 5 mg/kg/day. Throughout the clinical process, the daily dosage was increased by 5 mg/kg/day till a 25 mg/kg/day dosage limit was attained | Reported seizure frequency and severity of seizure activity. | Epilepsy Treatment OutcomesFour children (17%) became seizure-free after 3 months, where one of the three patents was initially diagnosed with Dravet Syndrome. Patients entering the study with Dravet Syndrome had a greater than 50% probability of a reduction in seizure activity and 40% general reduction from median baseline characteristicsAllergic outcomes in ChildrenSignificant side effects were established from the administration of CBD-based treatment to the children with treatment-resistant epilepsy.  |
| **Overall conclusion:** There was a strong effect of CBD enriched oil extract on greater than 50% probability of a reduction in seizure activity and 40% general reduction from median baseline characteristics |

## **Table 6:** *Studies Investigating the Efficacy of CBD Treatment of Intractable Epilepsy*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Subjection to CBD treatment Interventions** | **Outcome measures** | **Results**  |
| Neubauer et al. (2018) Clinical Trial | To investigate assessed the efficacy of add-on therapy adopting CBD in the treatment of refractory epilepsies among children | The clinical trial included 66 children with onset refractory epilepsy were selected from the Centre of University Children’s Hospital Ljubljana, Slovenia, and actively included within the research process | Add-on therapy with CBD was initiated on the patients.Throughout the research process, the applied dosage was gradually added to the minimum of 8mg/kg/day | Patients reported seizure frequency and severity of seizure activity. | Epilepsy Treatment OutcomesResults revealed that 32 patients (48.5%) experienced a 50% improvement in seizure frequency, whereas 14 patients (21.25%) became seizure-free after clinical procedures.Less aggravated seizures, shorter seizure periods, and reduced periods to recovery.Although no patients reported adverse effects of CBD treatment on seizure activity, the CBD administration did not affect 15 patients (22.7%) |
| **Overall conclusion:** There was a significant effect of cannabidiol based intervention on the reduction of seizure frequency where 14 patients (21.25) became seizure-free after the clinical procedures.  |

## **Table 7:** *Studies Investigating the Efficacy of CBD Treatment of Intractable Epilepsy*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Subjection to CBD treatment Interventions** | **Outcome measures** | **Results**  |
| Kaplan et al. (2017) Clinical Trial | To investigate the application of cannabinoid-based treatment of refractory epilepsy, especially Sturge-Weber syndrome among affected patients within the contemporary medical settings | Five patients with Sturge-Weber syndrome brain conditions and intractable epilepsy (N=5). | Add-on therapy with CBD was initiated on the patients.Throughout the research process, the applied dosage was gradually added to the minimum of 8mg/kg/day | Measures of CBD effectiveness include the frequency of seizure activity, the general quality of life, and adverse effects during the pre-treatment and treatment period.  | Epilepsy Treatment OutcomesFindings indicate that 2 subjects and 3 patients reported a 50% reduction in seizure activity at week 14 and the last period, respectively. All 5 patients reported a significant improvement in their quality of life and therefore continued the use of cannabidiol throughout the 63rd to 80th weekAdverse EventsMild mood side effects arising from the usage of cannabidiol |
| **Overall conclusion:** There was a strong influence of CBD enriched treatment on the reduction of seizure frequency and improvement of life quality of children suffering from intractable epilepsy |

## **Table 8:** *Studies Investigating the Efficacy of CBD Treatment of Intractable Epilepsy*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Subjection to CBD treatment Interventions** | **Outcome measures** | **Results**  |
| Press et al. (2015)Retrospective Chart Review | To investigate the explored the efficacy of oral cannabis extracts (OCE) on the treatment of epilepsy within conventional medical settings. | Seventy-five patients were included within the study (N=75) | Oral cannabis extracts (OCE) were adopted the treatment of epilepsy within conventional medical settings. | Measures responder rate (%) Treatment outcomes  | Epilepsy Treatment OutcomesResponder rate for CO and OCE compared as 47% vs 22% respectively. Further, the variation present within the responder rate was based on the nature of epileptic syndromes where; Dravet 23%, Doose 0%, and Lennox-Gastaut syndrome (LGS) 88.9%. Positive outcomes established from the system-wide implementation of OCE for epilepsy treatment include improved motor capacities (10%), higher alert behaviour (33%), and improved language (10%). |
| **Overall conclusion:** There was a strong effect of CBD enriched treatment on the responder rate and improvement of life quality of children suffering from intractable epilepsy.  |
|  |
| **Table 9:** *Studies Investigating the Efficacy of CBD Treatment of Intractable Epilepsy* |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Subjection to CBD treatment Interventions** | **Outcome measures** | **Results**  |
| Devinsky et al. (2017)Randomized control trial (RCT) conducted by  | To investigate the application of cannabinoid-based treatment of refractory epilepsy, especially Sturge-Weber syndrome among affected patients within the contemporary medical settings | Double-blind, placebo-controlled trial, children diagnosed with Dravet syndrome epilepsy were subjected to a. Further, the patients were provided with the standard antiepileptic treatment.  | Cannabidiol (CBD) dose of 20 mg per kilogram of body weight per day or placebo | Measure of the change in seizure activity and frequency was recorded over a 14-week treatment period.Compared with a 4-week baseline period.  | Epilepsy Treatment OutcomesDecrease in convulsive seizures per month from 12.4 to 5.9 using cannabidiol treatment as compared to a recorded decrease of 14.9 to 14.1 with placebo 43% of the patient population reported a greater than 50% reduction in the frequency of epileptic seizures using cannabidiol as compared to 27% of the patient population in the placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08).  |
| **Overall conclusion:** There was a strong effect of CBD enriched treatment on the reduction of convulsive activity and improvement of life quality of children suffering from intractable epilepsy.  |

## **Table 10:** *Perceived Efficacy of Cannabidiol enriched treatments*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Cannabidiol Treatment Intervention** | **Outcome measures** | **Results**  |
| Porter and Jacobson (2013) Open-label TrialParent survey | To examine the application of cannabidiol based treatment for assisting children with intractable epilepsy | 19 participants were included where 13 children has Dravet syndrome, four had Doose syndrome, and one had Lennox-Gastaut syndrome and idiopathic epilepsy (N=19).  | Cannabidiol bases treatment | Seizure activity and frequency | Treatment OutcomesSixteen parents (84%) reported a significant reduction in the occurrence of seizures while applying CBD based treatment.Two parents (11%) reported the total treatment of seizures rendering their children seizure-free. Eight parents (42%) indicated a higher reduction in seizure activity up to 80% while six (32%) reported a 25-60% reduction in frequency of convulsions. |
| **Overall conclusion:** There was a strong effect of CBD enriched treatment on the reduction of seizure frequency and improvement of life quality of children suffering from intractable epilepsy |

## **Table 11:** *Perceived Efficacy of CBD Treatment of Intractable Epilepsy*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year and study design** | **Aim of the study** | **Sample size and characteristics** | **Cannabidiol Treatment Intervention** | **Outcome measures** | **Results**  |
| Hussaini et al. (2015) Open-label TrialParent survey | To investigate the perceived efficacy of cannabidiol treatment of paediatric epilepsy, especially the treatment of infantile spasms (IS) and Lennox-Gastaut syndrome (LGS)  | Online survey of 117 parents of children with epilepsy (including 53 with IS or LSG) (N=117) | The average duration and dosage for administration of CBD treatment to refractory patients were 6.8 months and 4.3mg/kg/day respectively. | Perceived efficacy, dosage, and tolerability of CBD in the treatment process85% of the parents reported a significant reduction in seizure frequency, whereas 14% reported seizure-free children after using the CBD treatment. | Treatment Outcomes85% of the parents reported a significant reduction in seizure frequency, whereas 14% reported seizure-free children after using the CBD treatment. |
| **Overall conclusion:** There was a strong influence of CBD enriched treatment on the reduction of seizure frequency and improvement of life quality of children suffering from intractable epilepsy |

# Discussion

The primary aim of the current systematic review was to examine the medical influence of cannabidiol based intervention on the treatment of intractable epilepsy among children. Findings from the systematic review of data indicate the efficacy of cannabidiol in improving the treatment outcomes of children suffering from drug-resistant epilepsy. Multiple research studies and clinical trials report the positive influence of CBD based treatment on the reduction of seizure activity and general improvement of life quality among young patients with intractable epilepsy.

## *Cannabidiol Mechanism of Action*

From a broader perspective, CBD treats epilepsy through active interactions with natural cannabinoid receptors such as the serotonin receptors [5-HT], opioid receptors [ORs], and non-endocannabinoid G protein-coupled receptors (GPCRs) as well as ions channels and enzymes.

Neuroprotective attributes of CBD emerge from its anti-inflammatory and antioxidant properties, thereby can be used for improving neurological health status within medical practice. The mechanism of action adopted by CBD for appraising health outcomes of epileptic disorders focuses on the reduction of the convulsions and recurrence of epileptic seizures among patients. The therapeutic properties of CBD rely on the endocannabinoid signalling systems which encapsulates the G protein, CB­1, and CB2 endogenous receptors, which function to manage the metabolism neurological actions (Devinsky et al., 2017). While most phytocannabinoid actions within the neurological systems are medicated by either CB­1 and CB2 receptors, CBD reflects a low affinity for CB­1 and CB2 receptors. Research identifies the cannabinoid receptor-independence of CBD significantly contributes to its anticonvulsant effects (Hill et al., 2012 ).

Through the anticonvulsant capacity of CBD as well as its therapeutic effects, CBD actively inhibits epileptiform activity within the neurological composure, thereby reducing the seizure frequency and severity among affected individuals. The CBD treatment mechanism emanates from the antagonizing action of CBB on GPR55 at neurological synapses (Devinsky et al., 2017; Kaplan et al., (2017)). In essence, the inhibition of GPR55 attributes to the reduced release of intracellular calcium, thereby reducing the excitatory currents during neurological transmission, significantly reducing seizure activity (Devinsky et al., 2017). Through modulating the neurotransmission activity of GPR55, CBD limits the rapid increase in excitatory postsynaptic current among pyramidal neurons which may trigger convulsive activity in epileptic tissues. Further, CBD significantly reduces the TRPV1 channels, which contribute to the inhibition of extracellular calcium influx during the normal neurotransmission actions within the central nervous system (CNS). From a broader perspective, the treatment mechanism of CBD focuses on controlling the activity of neurotransmitters at the surface of every nerve cell. While the occurrence of seizures among patients suffering from epilepsy attributes to the significant rise of receptors on the nerve cell, CBD functions to stimulate and blocks the GPR55 receptors involved in seizure activity, which lose their inhibition (Kaplan et al., 2017).

## *Reduction of Seizure Frequency and Activity*

Six studies report the reduction of seizure activity by more than 50% among children with intractable epilepsy subjected to stable doses of CBD based treatments. Using CBD within epileptic treatments improves the general orientation and structure of the neurological systems thereby limiting the recurrence of epileptic seizures among the victims (Press et al., 2015: Devinsky et al., 2017; Hussaini et al., 2015; Kaplan et al., 2017; Porter and Jacobson, 2013).

Evidence indicates the capacity of CBD treatment in reducing the seizure burden among children suffering from drug-resistant epilepsy (Press et al., 2015: Devinsky et al., 2017; Hussaini et al., 2015; Kaplan et al., 2017; Porter and Jacobson, 2013). While examining the efficacy of add-on therapy adopting CBD in the treatment of refractory epilepsies among children, Neubauer et al., (2018) established that a significant number of patients reported less aggravated seizures, reduced seizure periods, and shorter periods of recovery among other positive outcomes from CBD treatment. Kaplan et al. (2017) report a 50% positive change in seizure activity at last study periods as well as the general improvement in the quality of life among the patients.

Parent survey by Press et al., (2015) illustrates the positive outcomes associated with CBD treatment of epilepsy which includes improved motor abilities, increased level of alertness, and better language communication. In essence, CBD was established to positively influence the treatment outcomes of Dravet 23%, Doose 0%, and Lennox-Gastaut syndrome (LGS) among children. Using a 4.3mg/kg/day CBD treatment for 7 months, Hussain et a., (2015) established a significant change in seizure frequency and activity, as well as total treatment of epilepsy over the long term. Positive outcomes associated with CBD enriched include better sleep outcomes, improved alertness, and improved mood among patients. Parent survey by Porter and Jacobson (2013) report the reduction in seizure activity among four patients with Doose syndrome, and one diagnosed with Lennox-Gastaut syndrome and idiopathic epilepsy. Additional health benefits from CBD therapy include higher alertness, improved sleep outcomes, and healthy moods. In essence, the application of CBD based treatment in epilepsy improves the general life quality of patients.

Devinsky et al. (2017) indicate a significant reduction in convulsive seizure activity within a month of administering cannabidiol treatment as compared to conventional treatment. In essence, the seizure activity and frequency of epileptic seizures were significantly reduced by 50% for a larger portion of the study population. Further, the study records seizure-free patients generated from the proper administration of CBD based treatment.

## *Adverse Events*

Three studies report adverse effects of CBD treatment of health domains of the patients, which include; fatigue, vomiting, discomfort, and liver disorientation (Devinsky 2017). Further, patients reported seizures and somnolence/fatigue (Press et al., 2015). There was an abnormal increase in appetite among 30% of the population subjected to CBD enriched treatment for epilepsy.

## *Evidence Quality Assessment*

Studies were significantly consistent in the approaches and variables adopted for testing the medical influence of CBD enriched treatments among intractable epilepsy patients. Childhood epilepsy outcomes for using cannabidiol treatments were measured through changes in seizure frequency and severity of seizure activity (Press et al., 2015: Devinsky et al., 2017; Hussaini et al., 2015; Kaplan et al., 2017; Porter and Jacobson, 2013). The quality of evidence from the measurements remains high, which attribute to the distinct identification of CBD influence on treating epileptic convulsions and associated health issues. However, there was inconsistency in the experimental measurements of CBD outcomes where Hussaini et al., (2015) and Porter and Jacobson, (2013) used parent survey for the exploration of effects of CBD treatments on seizure frequency and period to recovery.

In comparison with previously published research on the treatment of epilepsy, the evidence established from the review of eight studies significantly aligns with the earlier identification of the capacity of cannabidiol to improve treatment outcomes in epilepsy. Based on early research, cannabidiol therapy imparted positive outcomes on the treatment of epilepsy, however, a small portion of the study populations was positively affected. Further, the current review of studies remains consistent with earlier research on the potential side effects of cannabidiol treatment on the patients.

Although the review of the studies provides resourceful information on the efficacy of cannabidiol in the treatment of intractable epilepsy, there are significant limitations within the design and research approaches adopted in assessing CBD effects on treating epilepsy. A significant limitation remains evident in the variations in the countries in which the studies are conducted. For instance, Neubauer et al., (2018) examined the efficacy of CBD therapy among children at the Сenter of the University Children's Hospital Ljubljana, Slovenia while Devinsky et al., (2017) examined the United States population. Further, the studies adopted varying procedures for the administration of CBD intervention as well as different dosages. In essence, review and comparison of outcomes from varying administration process populations poses a significant challenge in the systematic review.

Future research within the study area should adopt multiple designs such as randomized, double-blind, Placebo-controlled designs for generating broad evidence on the effects of cannabidiol in the treatment of intractable epilepsy. While some studies report seizure-free patients after the usage of CBD enriched treatments (Devinsky et al., 2017; Hussaini et al., 2015; Porter and Jacobson, 2013), future research should perform longer trials with extended follow-up periods to establish the long terms influence of cannabidiol in alleviating epilepsy among children.

# Conclusion

Findings from the current systematic review reveal the significant influence of cannabidiol treatment therapies in improving the health outcomes of children suffering from intractable epilepsy. While pharmacological treatments on intractable epilepsy offer minimal positive outcomes, evidence indicates the influence of CBD's therapeutic and anticonvulsant properties in reducing the seizure activity, frequency of convulsions, and severity of drug-resistant epilepsy. The evidence remains sufficient that the application of cannabidiol based treatments holds a positive influence on reducing the seizure frequency and general epileptiform activity. The anticonvulsant properties of cannabidiol greatly influenced the recurrence of epileptic convulsions, thereby leading to a reduction in seizure frequency.

Through establishing the self-reported and measured outcomes on seizure frequency and activity among patients subjected to CBD treatment, the review acquires evidence for answering the PICOS question. From a broader perspective, the therapeutic and anticonvulsive properties of CBD play an integral role in appraising treatment outcomes among intractable epilepsy by reducing the frequency of convulsions. Additionally, evidence acknowledges the therapeutic effects of the quality of life, including improved moods and alertness among the patients. However, there is insufficient evidence on the ability of cannabidiol based treatments to completely cure the neurological disorder, thereby producing seizure-free patients, who initially suffered intractable epilepsy.

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# Appendices

# PICOS Question

**RQ:** In children with epilepsy, is cannabinoid compared with normal treatment, effective in reducing epileptic convulsions?

# **PRISMA-P 2015 Checklist**

**This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al.:** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4:1**

| **Section/topic** | **#** | **Checklist item** | **Information reported**  | **Line number(s)** |
| --- | --- | --- | --- | --- |
| **Yes** | **No** |
| **ADMINISTRATIVE INFORMATION** |
| **Title** Systematic Review of Cannabinoid  |
|   Identification  | 1a | Identify the report as a protocol of a systematic review | [x]  | [ ]  | 4 |
|   Update  | 1b | If the protocol is for an update of a previous systematic review, identify as such | [ ]  | [x]  |  |
| **Registration**  | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | [ ]  | [x]  |  |
| **Authors**  |
|   Contact  | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide the physical mailing address of the corresponding author | [x]  | [ ]  | 2 |
|   Contributions  | 3b | Describe contributions of protocol authors and identify the guarantor of the review | [ ]  | [x]  |  |
| **Amendments**  | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | [ ]  | [x]  |  |
| **Support**  |
|   Sources  | 5a | Indicate sources of financial or other support for the review | [x]  | [ ]  | 887 |
|   Sponsor  | 5b | Provide name for the review funder and/or sponsor | [ ]  | [x]  |  |
|   Role of sponsor/funder  | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | [ ]  | [x]  |  |
| **INTRODUCTION**  |
| **Rationale**  | 6 | Describe the rationale for the review in the context of what is already known | [x]  | [ ]  | 102 |
| **Objectives**  | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | [x]  | [ ]  |  |
| **METHODS**  |
| **Eligibility criteria**  | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | [x]  | [ ]  |  |
| **Information sources**  | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | **[x]**  | [ ]  |  |
| **Search strategy**  | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | [x]  | [ ]  |  |
| ***STUDY RECORDS*** |
|   Data management  | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | [ ]  | [ ]  | 245 |
|   Selection process  | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | [x]  | [ ]  | 229 |
|   Data collection process  | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | [x]  | [ ]  | 232 |
| **Data items**  | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | [x]  | [ ]  |  |
| **Outcomes and prioritization**  | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | [x]  | [ ]  | 302 |
| **Risk of bias in individual studies**  | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | [x]  | [ ]  | 324 |
| ***DATA*** |
| **Synthesis**  | 15a | Describe criteria under which study data will be quantitatively synthesized | [x]  | [ ]  |  |
| 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., *I* 2, Kendall's tau) | [x]  | [ ]  | 378 |
| 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | [x]  | [ ]  | 403 |
| 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | [ ]  | [x]  |  |
| **Meta-bias(es)**  | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | [ ]  | [x]  |  |
| **Confidence in cumulative evidence**  | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | [x]  | [ ]  | 278 |