

Helsevetenskapelige fakultet

Cannabinoid therapy for Epilepsy :

A literature review and a survey among neuro-paediatricians

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Preface

The aim of this thesis has been to investigate the use of cannabinoids in treatment of epilepsy. The idea came from the rising in attention in publicity and social media to patients with intractable epilepsy, that tried some sort of cannabinoid treatment with a positive outcome. These types of compounds have been regarded as without medicinal potential during most of the 20th century and due to political reasons, they have been hard to study. However, with the increasing number of anecdotal cases that showing encouraging results, there has been a resurging interest in cannabinoids.

Therefore, we set out to review the latest literature within the subject and also to perform an international survey to explore the knowledge and experience of caregivers in some countries of Northern Europe.

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Abstract

Background: The aim for this thesis has been to investigate the use of cannabinoids in treatment of epilepsy. The topic is currently under a lot of discussion in many countries, and there is a high pressure on the health community to make these substances available from both patients, their families and politicians. This thesis consists of two parts. First, I aimed to review the literature on this topic over the last 5 years. Secondly, we performed an international survey to investigate how much knowledge, clinical experience or perhaps lack of experience caregivers have on this topic.

Material and Methods: Clinical and medical databases were searched and the studies that matched inclusion/exclusion criteria were analysed. A web-based survey was sent out to neuro-paediatricians in Norway, Sweden, Denmark and Germany.

Results: The results from the literature show that especially cannabidiol (CBD) has an effect on seizure reduction, mainly shown in people with treatment resistant epilepsy (TRE).

We received response from 86 neuro-paediatricians, a low response rate (~14 %). Therefore, one can question how representative the results of the survey results are. However, the results indicate that a majority of caregivers argue that they do not treat patients that are in need of this treatment. Another issue seems to be that there is no product available, but mostly they also warrant studies to prove safety and efficacy. However, a lot of caregivers have come into contact with patients/families that have requested CBD treatment.

Conclusion: More placebo-controlled studies of CBD are needed, where it is also taken in account for these drug-drug interactions that have been shown and that there might be certain subgroups of epilepsy that benefit more than others.

The low response rate in our survey may indicate low interest for the topic. Or perhaps it will take some more years for interest to grow with the accompaniment of more compelling evidence.

1. Introduction

1.1 Background

It is estimated that > 50 millions of people live with epilepsy globally. That represents ~0.7% of the world's population, and 0.5 % of the total disease burden in the world. However, the incidence of epilepsy is not evenly distributed in the population. It is more prominent in people below 20 years and over 60 years, and also in people in developing countries (1, 2). Epilepsy was in the 1850s redefined as a neurological disease even though it was still considered a psychiatric condition. Today epilepsy is no longer considered to be a psychiatric condition but as a chronic neurological condition (1).

Different antiepileptic drugs (AEDs) are used to treat epilepsy, and many patients respond favourably. However, most AEDs have different adverse effects that have been found to impact quality of life. Retention rates have been shown to be equal among first and second-generation AEDs, despite different side effect profiles. Many parents express specific concern about cognitive side effects of AEDs (3).

Among children with epilepsy, there exist a subset of patients whose families are choosing to pursue alternative therapies, either instead of or in combination with conventional AEDs. Many of these patients have refractory epilepsy and have failed to gain control of their seizures after trials of many medications and interventions. Oral cannabis extracts (OCEs) are being used in the treatment of epilepsy with increasing rates in the United States following product legalization. However, the scientific documentations of clinical efficacy of OCEs has been limited or absent (3).

1.2 Definition of Epilepsy

Epilepsy is defined as an ongoing neurological condition that is characterised by spontaneous recurring high-frequent synchronised overexcitation in the brain that is manifested as a periodic seizure (1, 2). In an instruction manual for operational classification of seizures by Fischer et. al in 2017 , seizures are generally divided depending on onset. Focal onset, generalized onset and unknown onset are described. Subcategories like motor (convulsive) or non-motor component, awareness or impaired awareness and absence are a few of them. See Figure 1 for overview (4).

Most people think of generalized tonic-clonic seizures when they think of epileptic seizures, and they may be characterised by convulsions. However, epileptic seizure attacks without obvious (motor) convulsions are also common. There can be a lot of different types of combinations of seizures, and some seizures types, for example tonic seizures or epileptic spasms, can have either a focal or generalized onset. Also, level of consciousness or altered consciousness is a confusing concept even though central to many seizures (1, 4),

In a 2015 a new definition of status epilepticus (SE) was presented by The International League Against Epilepsy (ILAE) (5). SE was considered as a condition resulting from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormal, prolonged seizures. It is a condition, which can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures (5).

1.2.1. Epidemiology of Epilepsy

Epilepsy is one of the world's oldest recognized conditions, with written records dating back to 2800 BC in China (6). More than 50 million people worldwide have epilepsy, globally 2.4 million people are diagnosed with epilepsy each year. Epilepsy is a chronic disorder of the brain that affects people of all ages. In high-income countries, annual new cases are between 30-50 per 100.000 people. In low and middle-income countries these numbers can be up to two times higher (2). Six out of 10 people with epilepsy (PWE) have idiopathic epilepsy, with no identifiable cause. Epilepsy with a known cause is called secondary, or symptomatic epilepsy. Secondary causes can be:

- brain damage from prenatal or perinatal injuries (e.g. a loss of oxygen or trauma during birth, low birth weight).
- congenital abnormalities or genetic conditions with associated brain malformations.
- a severe head injury.
- a stroke that restricts the amount of oxygen to the brain.
- an infection of the brain such as meningitis, encephalitis, neurocysticercosis.
- certain genetic syndromes.
- a brain tumour.

In many parts of the world, PWE and their families suffer from stigma and discrimination (2).

1.2.2. Treatment of Epilepsy

There are a number of treatments for epilepsy. Around 70% of PWE can be successfully treated with AEDs and get seizures under complete control. Furthermore, after 2 to 5 years of successful treatment and being seizure-free, drugs can be withdrawn in about 70% of children and 60% of adults without subsequent relapse.

Globally there is a “treatment gap”. In low- and middle-income countries, about $\frac{3}{4}$ of PWE may not receive the treatment they need. Although it is possible to diagnose and treat most PWE at the primary health-care level without the use of sophisticated equipment (2). There are also some of the non-pharmacological treatment options such as ketogenic diet (KD), vagus nerve stimulation (VNS) and surgery (resective surgery, corpus callosotomy etc.). These treatment modalities have all been shown to be effective in selected patients.

Most AEDs have adverse effects that have been found to impact quality of life. Patients with treatment-resistant epilepsy (TRE) have often tried many different AEDs and risk both interactions and more adverse effects. Many parents express specific concern about cognitive side effects of AEDs (3).

1.2.3. Treatment-resistant epilepsy (TRE)

Approximately 30 % of PWE have refractory seizures even though they are on an “optimized” regimen with AEDs. There is however no currently valid definition of TRE. Usually when two separate medications have been tried, and you still have not achieved satisfactory treatment for the patient, they are referred to specialized care for further investigation. Although the number of AEDs on the market has continuously increased, it is not reflected in better control of seizures in patients with TRE (1). Even with all the different therapy available, less than 10% of patients with TRE become seizure free (7).

I will here present three different epileptic syndromes that often show treatment-resistance:

- **Dravet syndrome (DS)**, is a rare genetic form of epileptic encephalopathy, primarily due to loss-of-function mutations in the SCN1A-gene. It was described in 1978 by Charlotte Dravet. DS typically presents around 5-8 months of age with febrile seizures that progress to severe partial or generalized tonic-clonic seizures, and episodes of status epilepticus. It is more prevalent in males than females (2:1). The SCN1A gene encodes the alfa-subunit

in voltage-gated sodium channel type 1 (NaV.1.1) causing impaired firing of GABAergic interneurons, which results in an imbalance between excitation and inhibition that leads to seizures. The treatment of DS is generally combinations of AEDs and KD, but a large number remain treatment resistant (8).

- **Lennox-Gastaut syndrome (LGS)** is also a rare, severe form of epileptic encephalopathy with early childhood onset, usually manifests by 8 years with peak incidence between age 3-5. Patients are frequently treatment resistant to available medications. It is characterised by the occurrence of multiple seizure types, including so-called drop attacks (atonic, tonic, tonic-clonic seizures), slow spike-and-wave activity on electroencephalograms, and cognitive impairment. Few robust, population-based epidemiological studies of Lennox-Gastaut syndrome have been done, but regional studies (4-5) have reported that Lennox-Gastaut syndrome accounts for 1-4% of cases of paediatric epilepsy (7).
- **Tuberous sclerosis complex (TSC)** is an autosomal dominant genetic disorder with highly variable expression. TSC is caused by a mutation in the TSC1 and TSC2 genes, which encode for the hamartin and tuberin proteins, respectively. Normally, these proteins form a complex that acts as a tumour suppressor and a central regulator in the mammalian target of rapamycin (mTOR) signalling cascade. TSC is characterized by the presence of hamartomas in almost every organ system, including tubers and subependymal nodules in the brain (9). The most common neurologic symptom of TSC is epilepsy, which affects approximately 85 % of patients. Approximately 63 % develop treatment-resistant epilepsy (as opposed to 23% in the general epilepsy population). Around 8 in 10 experience their first seizure within the first 3 years of life, and 5 in 10 have more than one seizure type (9).

1.3. Cannabinoids

Derivates from the cannabis plant, *Cannabis sativa*, have long been used as a treatment for many disorders, from anorexia to pain. Ancient reports from early civilizations suggest that cannabis extracts can reduce seizures and was used from ~2800 BC in China until mid-1800s. in the western civilization (6).

There has recently been more attention paid to medical marijuana, in particular to strains that are high in cannabidiol (CBD) and low in tetrahydrocannabinol (THC), for the treatment of epilepsy. Animal studies have suggested that marijuana has potential

anticonvulsant properties. Independent action on endogenous receptors and ion homeostasis has been demonstrated (3), (10).

Chronic exposure to marijuana is associated with poorer cognitive outcomes, however there are few data available on the impact of chronic exposure to specific marijuana derivative products, especially in patients who already have cognitive delays (3).

1.3.1. Definition of cannabinoids

Cannabinoids can be defined as substances that bind to and activate the endocannabinoid receptors in the body. Cannabinoids are divided into i) phyto-cannabinoids, ii) endo-cannabinoids and iii) synthetic cannabinoids. Phyto-cannabinoids are extracted from the cannabis plant (*cannabis sativa*), endocannabinoids are produced in the body (Anandamide, 2-arachidonoyl-glycerol etc.) and synthetic cannabinoids are produced in laboratories (11). Cannabis extract contains a numerous of related effective substances, which are called cannabinoids. The two substances that are found in largest quantity is Δ^9 -tetrahydrocannabinol (THC) and its precursor Cannabidiol (CBD). CBD does not possess the psychoactive traits of THC and has shown anticonvulsive characteristics (11). Several preclinical and clinical studies suggest that CBD has anticonvulsant effects and is well tolerated (6), (12, 13).

1.3.2. Endocannabinoid receptors

The body's endocannabinoid receptors are part of the endocannabinoid system. The cannabinoid receptors are divided into CB1 receptor (CB1R) and CB2 receptor (CB2R). The CB1Rs are mostly localised in the central nervous system, while the CB2Rs are mostly localised in peripheral tissue. Both these receptors are G-protein coupled receptors (11).

There are large amounts of CB1Rs in the brain, with similar numbers of receptors for glutamate and GABA – which are the central excitatory and inhibitory neurotransmitters. CB1Rs in the brain are found primarily in the hippocampus, hypothalamus, cerebellum, the mesolimbic dopamine system, substantia nigra and cerebral cortex. Activation of the CB1R is what gives the psychoactive effects. CB1R is also found in peripheral tissue such as adipocytes, endothelial cells, and peripheral nerves. There is only a small amount of CB1R in the brainstem, which matches clinical findings that cannabinoids do not affect respiratory and cardiovascular function in such a large extent (11).

CB2R is found primarily in lymphatic tissue, such as the tonsils, spleen and lymphocytes that circulates the bloodstream. CB2Rs can also be found in the central nervous systems immune cells that are called microglia (11).

1.3.3. Presumed mechanisms of cannabinoids in the epileptogenesis

In the frontal lobe of the cerebrum there are large connected networks that can generate synchronised neural activity. However, if such activity occurs in excess in the cortical, hippocampal or thalamocortical networks, this can lead to epileptogenesis. The activity can also cause persisting changes in these neural networks which then can cause hyperexcitability, which we know as the pathology epilepsy (14). The endocannabinoid system is therefore an attractive target for therapeutic purpose since it has been shown that activation of it can affect the synaptic transmission between these neurons and thereby regulate the hyperexcitation within these networks (1). It has been shown that epilepsy modifies the endocannabinoid system (e.g. the CB1 receptor). Activation of CB1R, may as many other neuromodulating systems enhance or inhibit the time of seizures. Depending on the neuronal subpopulation involved (15).

In experiential models one has to be very certain on which type of neurons that are being observed/studied, to be able to determine whether CB1R in those specific surroundings show proconvulsive or anticonvulsive traits. It has become clear that CB1R is functional and is participating actively in the modulation and thereby regulation of epileptogenesis. With this knowledge, it also becomes possible to map down the anticonvulsive effect that cannabinoids have, also on different types of human epilepsy (14, 15).

Even though the results from the experimental models are relevant for the understanding of endocannabinoids role in epileptogenesis, they do not fully recreate the pathological conditions that occur in PWE. To study cerebral tissue collected from patients with TRE, which is made possible due to patients having epileptic surgery can be essential in the investigation of cannabinoids and the endocannabinoid system as therapeutic targets for PWE (15).

Research on the endocannabinoid system and its part in protecting neurons from developing epileptic pathology in animals, has provided us with new knowledge. Also, the long history of usage of extracts from cannabis plants might suggest that it could have anti-seizure effects under specific conditions (14).

2. Aim of the study

There are two aims of this thesis:

- Firstly, to review the literature over the last five years aiming to assess whether cannabinoids may have a role in treatment of epilepsy.
- Secondly, to perform a web-based survey aiming to obtain knowledge about clinical experience and perceptions on cannabinoid use for epilepsy among neuro-paediatricians in Norway, Sweden, Denmark and Germany.

3. Method and material

3.1. Literature review

My aim was to review literature published last 5 years on cannabinoid therapy for epilepsy. I used the PRISMA protocol for a systematic approach (16).

3.1.1. Criteria for including/excluding literature

Inclusion and exclusion criteria were determined for the review.

Inclusion criteria: Firstly, I included literature of clinical effects, animal trials and pharmacological of cannabinoids being used for studying anti-convulsive traits. Secondly, in order to get updated knowledge and to avoid too many articles we aimed for articles I included only articles published last 5 years.

Exclusion criteria: Articles about recreational cannabis smoking. Articles about cannabinoids used in other fields of medicine, such as pain control in multiple sclerosis or palliative cancer treatment. Articles focusing on the psycho-activity of different cannabinoid substances.

3.1.2. Search process

Using the PICO model for clinical questions, we defined what subjects on which our searches were to be performed (17). Epilepsy and children was the group of patients that were targeted. The intervention that we wanted to investigate was cannabinoid therapy.

The three subjects were defined to be cannabinoids, epilepsy and child. After these were confirmed, a couple of appropriate databases were identified in which searches on our three subjects firstly were performed on the individual subject, then cross referenced so that the result of our search would include our 3 subjects.

I performed searches in two databases: Ovid's MED-LINE and Ovid's EMBASE. The searches were performed on several occasions, but the last one was performed on the 06.04.18 on both MED-LINE and EMBASE.

3.2. International survey

As part of the thesis, a survey was also outlined on the topic of cannabinoid treatment of epilepsy in children. Our aim was to send it to neuro-paediatricians in Norway, Sweden, Denmark and Germany. We got help from colleagues in these specific countries for the distribution.

It is a short survey (16 questions, takes less than 5 min to answer) with the purpose of exploring and trying to map how much knowledge, clinical experience (or lack of experience) caretakers have about cannabinoids as treatment of epilepsy. We also asked to what extent patients (or families) have asked, for these kinds of treatments. Another interest point was if the caretakers had knowledge of patients with epilepsy self-medicating with cannabinoids. We used the online survey software Survey Monkey[®]. The system gathered the responses and produced analysis of the data. See survey attached.

4. Results

Literature review

In MED-LINE 111 articles were found in the cross-referenced search and 51 articles matched the inclusion criteria. In EMBASE 39 articles were found when the search was performed, and 11 were included after matching our inclusion criteria. In total with our two databases search I found 62 studies/articles/reviews. 26 studies were reviewed, the additional comprised

of reviews, brief communication that was used for background information and literature in books, that describe cannabinoids pharmacological mechanism's in relation to epileptogenesis, which are also used in the introduction.

The results of the literature review is presented according to the study design.

Randomised clinical trials (RCT) present strongest evidence, prospective cohort studies provide less strong evidence, and retrospective cohort studies or case-control studies provides lower quality of evidence. Cannabinoids effect are of interest despite not reporting clinical outcomes in human patients.

2 RCTs, 6 prospective cohorts, 3 retrospective cohorts, 9 animal/pharmacological studies and 5 international surveys were reviewed.

4.1.1 Clinical Trials

There were two RCTs published last 5 years. Both studies were multinational, double-blinded phase III trials. The trials consisted of one treatment group that got adjunctive CBD on top of their epilepsy treatment regimen versus a placebo group. The populations were DS patients (Devinsky, et al. 2017) and LGS patients (Thiele et al, 2018) (7, 18).

Their results for their primary endpoint indicated that CBD as an ad-on therapy was successful in reducing convulsive seizures. Other secondary endpoints, like quality of life, alertness and sleep pattern also was reported by their caregivers to be improved. In the LGS study there were 3 times as many patients/caregivers in the CBD group that reported improvement in the secondary endpoints than the placebo group. Some patients could also reduce their use of AEDs, however this was not only because of positive results of the therapy but also because of drug-drug interactions between some AEDs and CBD (7, 18).

During the treatment period three patients in the CBD group and no patients in the placebo group were free of seizures ($P=0,08$) in the DS-study (18). In the LGS-study three patients who were in the CBD group and completed treatment were drop-seizure free throughout the 12-week maintenance period (7). No patients in the placebo group were free of drop seizures in either studies (7, 18).

There were also some adverse effects which were more prominent in the CBD group compared with the placebo. Among patients with adverse events, the majority had events that

were mild or moderate in severity (diarrhoea, somnolence, pyrexia, decreased appetite and vomiting), however some serious adverse events occurred (7, 18).

In the DS study, status epilepticus was reported in three patients in each group, elevated levels of liver enzymes led to the withdrawal from the trial for three patients in the CBD group and 1 in the placebo group. All patients with elevated levels of liver enzymes were taking some form of valproate (18).

Sensitivity analyses from the LGS study confirmed that the treatment effect of cannabidiol on the primary endpoint was established during the first 4 weeks of the maintenance period and was maintained during the full treatment period. Sensitivity analyses of the three key secondary endpoints also showed significant treatment differences in favour of CBD (7).

Other clinical studies

I identified nine open-label prospective and retrospective cohort studies published between 2013-2018. Almost all of them focus on different specific epileptic syndromes, and how CBD (Epidiolex[®], GW Pharmaceuticals) or some other compound that is high in CBD and low in THC affects seizure control and quality of life. Many of the patients used several AEDs and other non-pharmacological treatments but still did not achieve seizure control (3, 9, 10, 19-22). I will present five of these studies in detail, and the last four only briefly in Table 1.

In one prospective cohort study (Hess et al, 2016, 18 patients who had TSC (TSC1 or TSC2 mutation) were followed. The primary endpoint was total weekly seizure frequency change. Patients were defined as responders if they had a > 50% reduction in total seizure frequency. After 3 months of CBD-treatment, there was a median 50% reduction in seizure frequency. Moreover, four patients had a > 80% decrease in seizures and two patients had 90% seizure reduction. Most adverse effects experienced in this study were temporary and of mild severity. Adverse effects were resolved through dose adjustments of CBD or concomitant antiepileptic drugs. The most common adverse effects cohere with profiles in other studies (9).

In one retrospective cohort study (Treat et al, 2017), oral cannabis extracts (OCEs) duration and discontinuation was measured in relation to perceived benefit by parents. Seizure response was based on a parental report of seizure frequency prior to initiating OCEs compared to the last documentation of seizure frequency while on OCEs. Of the 119 patients

included, 24% were considered to be responders to OCE treatment. LGS was the only syndrome type associated with a significantly higher proportion of responders when compared to all other patients in the cohort: 11 (58%) of 19 patients ($p < 0.05$). Perception of seizure benefit was shown to be the only significantly associated factor with longer duration of OCE use ($p < 0.01$). The only syndrome that emerged to have a significant impact on duration of OCE use ($p=0.02$) was DS, which was associated with a shorter duration of OCE use. Adverse events due to OCE treatment were reported by parents of 23 patients (19%). The presence of adverse events was significantly associated with faster discontinuation of OCE treatment ($p = 0.03$). Eighty-four patients (71%) discontinued their OCE use during the study period (3).

In another open label interventional (Devinsky et al. 2016) trial patients with severe, childhood-onset TRE were studied at 11 epilepsy centres across the US. The most common epilepsy syndromes treated were DS and LGS. The primary endpoint was to establish the safety and tolerability of CBD, and the primary efficacy outcome was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. The median change in total seizures was -34.6% (IQR $-66,7$ to $-9,8$). Two patients were free of all seizure types over the entire 12 weeks. Analysis of the secondary endpoints of responder rates showed that 54 (39%) patients had a reduction of 50% or more motor seizures. Most adverse events were mild or moderate and transient. Serious adverse events were reported in 48 (30 %) patients. Serious adverse events deemed possibly related to CBD use were recorded in 20 patients and included status epilepticus, diarrhoea, pneumonia, and weight loss. Eleven (7%) patients had elevated liver function tests, one patient had a significant increase in transaminases leading to discontinuation of CBD. The adverse event profile of CBD was favourable, with most patients tolerating the drug well despite its addition to a median of three concomitant antiepileptic drugs (10)

In an observational, longitudinal study (Hausman-Kedem et al. 2018) the effect of cannabinoids on TRE was assessed. Forty-six patients were included in the efficacy analysis. 56% had a reduction of 50% or more in all seizure types. 19 patients partially or completely tapered 1-3 AEDs. AEs occurred in 46 % of patients. Improvement of AEs came with time or dose reduction. A beneficial response such as improvement in behaviour, communication, sleep and spasticity was reported in 23% of patients (19).

An expanded access investigational new drug study (Geffrey AL, et al, 2015) focused on the safety and efficacy of CBD (Epidiolex[®], GW Pharmaceuticals) as a new adjuvant treatment for refractory epilepsy in 25 children. Pharmacokinetic analysis of clobazam (CLB) in previous clinical trials has demonstrated that there is a clinically significant drug-drug interaction when CLB is taken with strong or moderate CYP 2C19 inhibitor. Interaction between CBD and CLB in the 13 children who are taking both drugs concomitantly was also evaluated. Nine of the 13 subjects had a > 50% decrease in seizures, corresponding to a responder rate of 70%. Over the course of CBD treatment, CLB dose were reduced for 10 (77%) of the 13 subjects. The mean change in seizure frequency for the 10 subjects with lowered CLB doses was a 50 % decrease, whereas the mean change for those without was a 55% decrease. Side effects were reported in 10 (77%) of the 13 patients. These 10 subjects experienced drowsiness (n=6), ataxia (n=2), irritability (n=2), restless sleep (n=1), urinary retention (n=1) and loss of appetite (n=1). All side effects were resolved with CLB dose adjustments. All study objects continued to tolerate CBD well at time of data analysis (week 36 of treatment (23).

Table 1 shows four more clinical studies made between 2013-2018.

4.1.2. Pharmacological studies and Animal Trials

The antiepileptic mechanisms of CBD have not been fully elucidated and is considered to be mediated by inhibiting excitatory glutamatergic neurotransmission, mostly via cannabinoid receptor-independent mechanisms. Other properties of CBD, including neuroprotective, anti-inflammatory and antioxidant properties have been described (24). Nine studies investigating CBD-pharmacology studies or animal CBD studies are described in Table 2 (8, 25-32).

4.1.3 Previously published international surveys

Five publications from surveys relative to the topic were identified in our searches (33-37). The surveys were constructed seeking opinion, knowledge and experience from PWE, their families or caregivers about usage of cannabis products in treatment of epilepsy. They were of different sample sizes, patients used different kind of cannabis products (e.g. CBD-enriched cannabis, Real scientific hemp oil = RSHO-X[®]) and took place in different countries (e.g. US, Mexico, Australia). Some of these cannabis products were approved by the countries

medical agencies, this of course makes a difference in how easy it is to purchase products and knowing the quality of them.

Web-based applications were mostly used to collect the survey data (REDCap, SurveyMonkey® etc.). Some of the surveys had clear endpoints defined, e.g. response rate of > 50% seizure rate, whilst others just reported a reduction of seizure frequency not specifying how big the rate of seizure reduction was. In general, the results from the surveys were positive, and benefits in quality of life, emotional state, communication, sleep patterns and diet were also reported.

One of the studies tried to identify predictors for cannabis use and against. Here the number of past used AEDs was a significant predictor of cannabis product use, and the uncertainty of the product quality and how to get at hold of it was a predictor against use. However, over 55% of the study sample reported willingness to participate in medical research studies in medicinal cannabis (33-37).

4.2. International survey on cannabinoid treatment of epilepsy in children.

Our survey was sent out to neuropaediatricians in four countries. 300 members in the neuro-paediatric association in Sweden, 149 neuro-paediatricians in German, 124 members of the neuro-paediatric association in Denmark and 50 neuropaediatricians in Norway. We got 85 responses in total which gives us a response rate of 13.6%.

The responders were almost equally distributed in gender with 42 females (49.4%) and 43 males (50.6%). Also, the distribution of responses in regard to country of practice were representative (although low response rate). Table 3 shows how the responders age and Figure 2 the responder's country of practice.

The work experience generally in the field of neuropediatric was high, almost half of them had over 15 years of experience. Fifty-six out of 85 responders (66%) answered that they treat children with epilepsy at least every week. Moreover, 80 caregivers (96%) had heard about of the use of cannabinoids in treating epilepsy in children. Forty-seven (60%) knew that CBD is the component of cannabinoids that is suggested to be most important for anti-epileptic activity. Only ten caregivers had personally prescribed cannabinoids for treatment of children with epilepsy, which was 12% out of the 80 who responded to the question. For the ones that had not prescribed cannabinoids on indication of epilepsy we

asked for their reasons (Figure 3). In open field answer the most frequent response, was that they had not felt the necessity of using the therapy for their patients. But there were also a lot of answers that suggested to wait for more studies of safety and efficacy. There were also answers that implicated that they were waiting for their national medical products agency to approve the medications first. The ones that had prescribed cannabinoid products, had mostly prescribed CBD oil, or Epidiolex[®]. The indications on which they had prescribed cannabis products is shown in Figure 4.

Perceived among caregivers that had prescribed cannabinoids is shown in Table 4. We also asked for adverse effects when prescribed cannabinoids, and lethargy/drowsiness and gastrointestinal symptoms e.g. diarrhoea and vomiting were the most frequent.

Finally, we aimed to ask the caregivers how they appreciate that the “climate” is for these substances. Forty-nine out of 71 have had patients or family of patients requesting cannabinoid therapy. Over 40 % of caretakers are aware of cannabinoid self-medication (not prescribed by a doctor). There were not many of caregivers that had prescribed cannabinoid therapy on any other indication than epilepsy.

5. Discussion

This review, was first intended to be a systematic review based on the PRISMA-P guidelines these last 5 years. We focused on 25 studies (eleven clinical studies, 9 animal and pharmacological studies and 5 survey studies) that matched the inclusion and exclusion criteria.

In addition, there were over 20 reviews identified in our search and over 10 communications with anecdotal stories of cannabinoid efficacy (6, 13, 21, 24, 38-60).

It could be argued that this is an indicator of cannabinoid treatment in epilepsy currently being a subject of intense current interest in its field. The public, through social media and news are becoming more and more aware of it. Clinical physicians, will increasingly have to answer questions and guide patients in the use of medical cannabis and consider the potential risks and benefits of this treatment.

The studies were of heterogenous study methods. The RCTs showed postintervention reductions in the primary outcomes, and there were open-label trials that although lack of blinded control groups (which limits the quality of evidence) also reported results that agrees with the results from the RCTs. Secondary endpoints, which in a lot of the studies (clinical and surveys) comprises of different scales of measuring other benefits like quality of life, alertness, cognitive function also showed improvement.

The animal, pharmacological studies have not proved the full mechanism in which CBD has reductive capacity in regard to seizures, but in vitro and in vivo models (which of course are not the same as in humans) the results speak for themselves.

One thing that must be defined and taken into account is that in a lot of these studies there is not a standardised cannabis product. Most of researchers and clinicians agree that the composition of the product that ought to be used should be almost solely CBD. Some of the surveys and cohort studies do not discriminate between cannabis product and this gives a wrong perception of efficacy and adverse effects profile. The consensus seems to have evolved into being that CBD is the compound that has seizure reductive traits to it. Therefore, the continuance of this discussion we will focus on the CBD products (Epidiolex[®], RSHO-X[®], enriched-CBD oral solutions etc.)

There are also many adverse events. The most common seem to be somnolence, diarrhoea, pyrexia, vomiting, decreased appetite. However, a lot of them seem to be mild or moderate in proportion, and in most cases, they get resolved by dose-control.

There was however, some serious adverse events in CBD studies. One example is the drug-drug interactions that it displayed with concomitant AEDs that patients took. Multiple studies have shown there is interactions between CBD and CLB (or it's active metabolite N-desmethyloclobazam). This is due to CBD's potent inhibition of CYP2C19, which is responsible for the metabolism of N-desmethyloclobazam. One study also showed that CBD interacts with topiramate, zonisamide, eslicabazepine and rufinamide (26). In the cases of patients of these studies that used Valproate or some form of it, elevated levels of ALT/AST after CBD treatment became so serious that they discontinued CBD treatment. Researchers also speculated that the delivery vehicle (sesame oil) could have been contributing to these

interactions. Nonetheless, patients seem to tolerate CBD well (23, 26). All these interactions need to be taken in account for if it in the future will be a possibility of treating PWE with CBD. However, like the surveys and other studies report, there is already a lot of people using some of these products and maybe their physician does not know about this, which can have terrible consequence.

This leads us to another point, the AEDs. Pointed out earlier in this review, a lot of the patients with TRE have often tried out a lot of different combination and may medicate with several AEDs. Patients, and parents turn to other treatment options when these do not control the seizures or perhaps have terrible side-effects. Polypharmacy is a real struggle in this patient group. This is also reported as a reason why patients turn to cannabinoids (34). The decision-making process for families regarding use of cannabis products for the treatment of paediatric epilepsy is not well understood. Particularly in children with severe epilepsy, families may turn to nonstandard treatments out of frustration with conventional medications and therapies (3).

In one of the survey, it was established a correlation of a stronger belief in the efficacy of CBD in patients with families that had relocated to a state where medical marijuana is legal. Parents who had relocated to Colorado were more than twice as likely to report a 50% reduction in seizures than were those who were long-time residents (47% vs 22%) (37). This is a problem with all of these studies in general. The ones that report seizures and other results are human, and often parents, or people close to the patients. How big the subjective bias is, is hard to determine. The issue of the placebo response is especially relevant in paediatric trials of cannabis-derived treatments. A placebo effect is also more concerning with cannabis-based preparations than with other antiepileptic drugs because of the intense media and family interest in the compound. It could also be a result because of parental belief in cannabidiol benefits because of high expectations (10). What is seen in studies is that parental perception of benefit of OCEs on seizure profile is a key driver of continued use of OCEs. Because many of the studies are retrospective, recall bias is another issue (3).

It is difficult to discern whether improved quality of life (QOL (which is reported in almost every study) results primarily from direct medication effects, reduced seizures, or

psychological benefits of reduced seizures, as each factor independently contributes to QOL, but the effects are not easily dissociable (21).

Our survey gives us an impression of the situation in Norway, Sweden, Denmark and Germany. It seems to be that there are a lot of hinders for caregivers to prescribe CBD. To begin with almost half of the responders argue that there are no patients that are in need of the treatment. Another issue seems to be that there is no product available, but mostly they also warrant studies to prove safety and efficacy. However, a lot of caregivers have come into contact with patients/families that have requested CBD treatment.

Limitations of the literature review is among others that the PRISMA guidelines were not fully met by this review (it can be argued that there were limitations to the study selection, summary measures and the risk of bias across studies). Lack of group for comparison and lack of blinding in most studies is also a big limitation.

To our own survey the biggest limitation is the low response rate. Thus, we do not know whether the results are not very representative. One can speculate, that the Nordic countries might be a bit conservative and the topic is too progressive or controversial. Despite a low response rate, the issues that came up in our survey, are resonating in the literature. The research community is making progress though, since 2013 clinical studies have multiplied, and at present there are about 25 ongoing clinical trials studying the effect on seizure frequency of CBD-enriched products, as well as their safety and drug interactions (24).

6. Conclusion

Use of cannabis products, especially CBD seems to have an effect on seizure reduction, most shown in people with TRE. However, the results vary, and so far, there is not a good enough understanding of adverse event profile, or true efficacy. Still, people with TRE might not have very many options and for those cases CBD should absolutely be therapeutic option.

Rigorous prospective placebo-controlled studies of CBD are needed, where it is also taken in account for these drug-drug interactions that have been shown and that there might be certain subgroups of epilepsy that benefit more than others. This thesis already misses out on new RCTs published very recently.

The result from our survey indicates that even though many of the responder had heard about cannabinoid therapy, this therapy is not widely used in the Nordic countries and Germany.

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8. Tables

Table 1. Clinical trials of cannabinoid therapy not described in the text of the thesis.

Article, country	Study design, sample size	All seizure red. > 50%	Mild to moderate AEs/Serious AEs	Treatment period / Compound
Tzadok et al. 2016 Israel (20)	Retrospective cohort, 74 patients	52% of cohort	29% / 18%	Median of 5.5 months / CBD:THC 2:1
Rosenberg et al. 2017, US(21)	Prospective open label, 48 patients	41,7% of cohort	58% / 20%	12 weeks / Epidiolex, CBD
Gofsheteyn et al. 2017, US (22)	Prospective open label, 5 patients	Was reported as collective 65% decrease in seizure frequency	40% /-	48 weeks / Epidiolex, CBD
Ladino et al. 2015 Canada (61)	Retrospective cohort,18 patients	Was reported as decrease in seizure frequency of 54 %	11% /-	6 months, Medical marijuana or street bought marijuana

Table 2. Pharmacological and animal studies.

Article, Country	Hypothesis Research question	Study design	Intervention	Results
Rubio et al. 2016, Spain (8)	Is there dysregulation in endocannabinoid system in DS patients?	Comparing gene expression DS patients to control patients.	qrt-PCR ¹ analysis of gene-expression of transmitter receptors etc.	Elevated gene expression for the CB ₂ receptor, in DS lymphocytes, without increased endocannabinoid levels in plasma.
Patel et al. 2016, US (25)	Is it possible to target resurging sodium current in mutated Na _v 1.1 and Na _v 1.6 as therapeutic strategy with CBD.	Comparing sodium currents in different variations of Sodium voltage channels and also if CBD had impact on them.	Mutations were introduced in HEK ² cells. The cells were with measurements of current where done	Mutation Na _v 1.1 that result in DS did not alter peak resurgent current. However, Na _v 1.6 which result in severe infantile

			before and after CBD intervention.	epilepsy dramatically increases peak resurgent current.
Gaston et al. 2017, US (26)	Are there interactions between CBD and AEDs.	Prospective open- label.	CBD was started in a group of 39 adults and 42 children, and interactions were identified and measured.	Significant increase in N- desmethylclobazam, Eslicarbazepine, Topiramate, Zonisamide and Rufinamide
Klein et al. 2017, US (27)	Does CBD have protective traits in treatment resistant epilepsy.	Evaluation of mice that were treated with CBD in regard to seizure protection.	The mice/rats were induced in seizures and treated with CBD to the point they became seizure protected. (what dosage, but also different types of phases, acute or more chronic types of states for the mice).	CBD exhibits anti- seizure properties, dose-dependent in acute seizure models.
Rowley et al. 2017, US (28)	Does CBR have a role to play in the down modulating seizures?	Controlled trial that compared mice with different setups of CBRs.	Mice were created without CBR ₁ and CBR ₂ or without both and then seizure activity was compared.	Results indicates that epileptic seizures in CBR double knock-out mice was much more prevalent than in single CBR knockout mice.
Huizenga et al. 2017, US (29)	Do CBR agonist have anticonvulsive effects?	Controlled trial comparing different compounds effect as seizure redactors.	DMCM ³ was given to rats with treatment with either agonist or antagonists of CB _{1/2} , CB ₁ , CB ₂ .	The mixed CB _{1/2} agonist and the CB ₁ agonist showed anticonvulsant effects against clonic seizures.

Di Maio et al. 2015, US (30)	Does treatment with an CB ₁ receptor agonist, WIN 55,212-2 ⁴ prevent brain damage after SE	Controlled trial, looking at the effects of WIN 55,212-2 in rats with induced SE	Different groups, two that received SE induction and one with WIN 55,212-2 treatment.	Results indicate that the anticonvulsant efficacy of cannabinoids is mediated primarily by CB ₁ R mediated modulation of glutamate and GABA release.
Carletti et al. 2015, Italy (31)	What are the anti-epileptic effects of WIN 55,212-2 and 7NI ⁵	Controlled trial, looking at the effects of WIN 55,212-2 and 7NI in rats with induced SE.	Control and treatment groups with pilocarpine induced general seizures and therapy with WIN 55,212-1 or 7NI.	Both WIN 55,212-2 and 7NI proved their ability to modulate epileptic phenomena with a neuroprotective effect.
Amada et al. 2013, UK (32)	Evaluate effect of CBDV ⁶ on PTZ ⁷ -induced increases in epilepsy.	Controlled trial.	Mice that were treated with CBDV were challenged with PTZ.	The results provide the first molecular confirmation of anticonvulsant effects by CBDV.

¹ qrt-PCR = quantitative real-time PCR

² HEK = Human embryonic kidney

³ DMCM = methyl-6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate, a chemo-convulsant

⁴ WIN 55,212-2 = An aminoalkylindole derivative, with effects similar to those of cannabinoids

⁵ 7NI = 7-Nitrodazole, a preferential neuronal nitric oxide synthase inhibitor

⁶ CBDV = Cannabidivarin, another phytocannabinoid

⁷ PTZ = Pentylenetetrazole

Table 3. International survey: Responder's age:

ANSWER CHOICES	RESPONSES
30-39	9.41% 8
40-49	30.59% 26
50-59	34.12% 29
60-69	22.35% 19
70-79	3.53% 3
TOTAL	85

Table 4. International survey: Caregiver's perceived efficacy, among those who had prescribed CBD therapy.

ANSWER CHOICES	RESPONSES
Moderate seizure burden reduction (> 50%)	36.36% 4
Good seizure burden reduction (> 90%)	0.00% 0
Shortening of seizures	9.09% 1
Less severe seizures	36.36% 4
Better life quality	36.36% 4
Improvement of cognitive ability	18.18% 2
No obvious effects	36.36% 4
Total Respondents: 11	

9. Figures

Figure 1. An overall classification model, taken from Fisher et al. 2017.

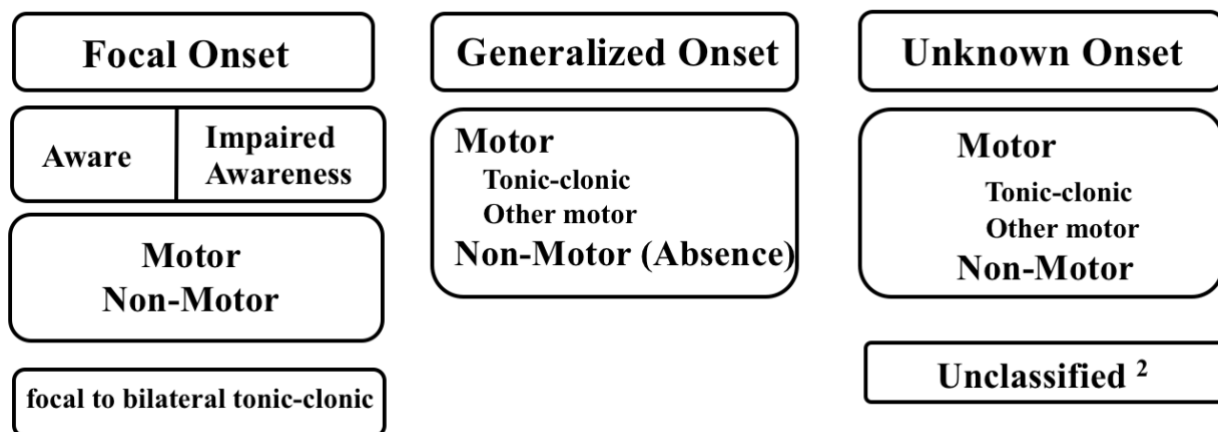


Figure 2. International survey : Country of practice

Answered: 85 Skipped: 0

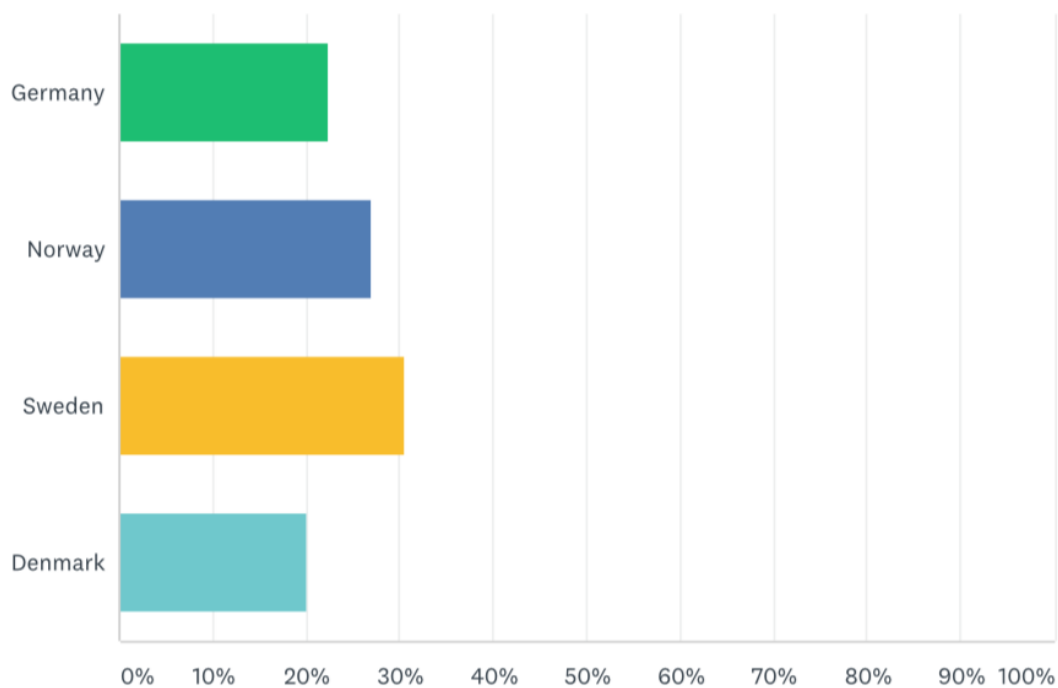


Figure 3. International survey: Why caregivers had not prescribed cannabis products.

Answered: 73 Skipped: 12

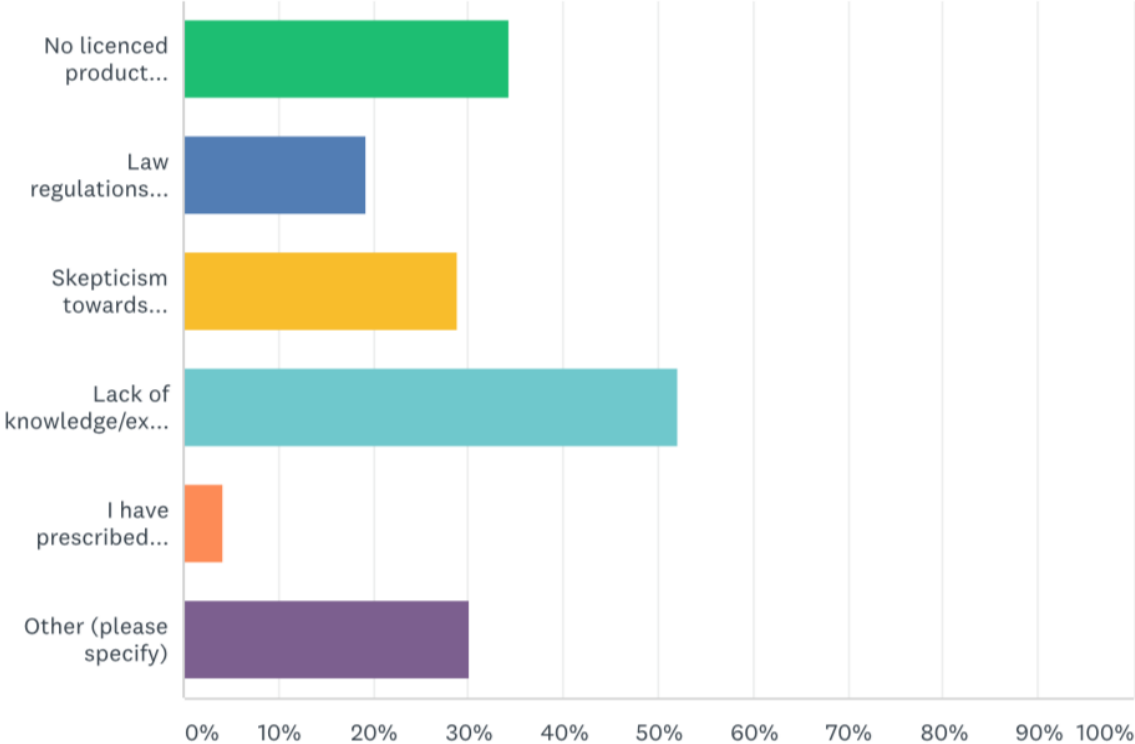
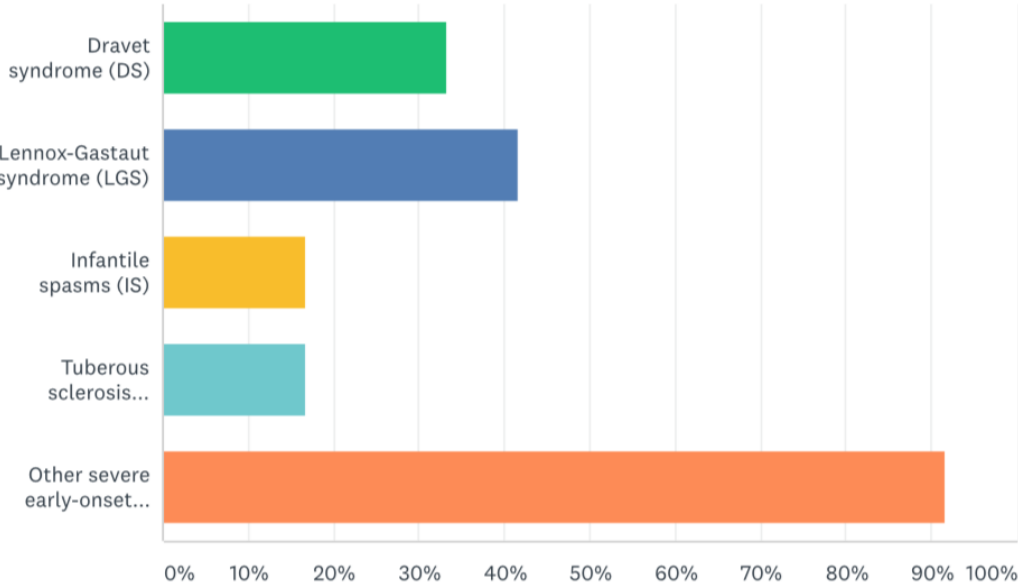


Figure 4. International survey: What indication cannabis products have been prescribed by the respondents.

Answered: 12 Skipped: 73



10. Attachment “ International survey on cannabinoid treatment of epilepsy in children”

International survey on cannabinoid treatment of epilepsy in children

Dear Colleague

Over the last decades there has been reports on the use of cannabinoids to treat children with epilepsy. Different cannabinoid formulations has been used that contains different amounts of tetrahydrocannabinol (THC) and cannabidiol (CBD).

We are conducting this international online survey among neuropaediatricians in Norway, Sweden, Denmark, Germany. The purpose is to investigate caretakers knowledge, attitudes and experiences (or lack of) with cannabinoids for treatment of epilepsy in children and adolescents (< 18 years of age).

We greatly appreciate your participation in this short online survey, which we expect to take no more than 5 minutes to complete. Replies will be treated in confidence and results made public in summarized form only.

Thank you in advance

George Mosulet, Bjørn Bjurulf, Thorsten Gerstner, Helle Hjalgrim and Claus Klingenberg,

Tromsø, Norway
Gothenburg, Sweden
Copenhagen, Denmark
Arendal, Norway

Background data

* 1. Gender

- Male
- Female

* 2. Age

30-39

60-69

40-49

70-79

50-59

* 3. Country where you work

Germany

Norway

Sweden

Denmark

* 4. Work experience with epilepsy

I see and treat children with epilepsy at least every week

I see and treat children with epilepsy at least every month

I do not regularly treat children with epilepsy

Other (please specify)

* 5. Work experience in the field of neuropaediatrics

0-4 years

5-9 years

10-14 years

15 years or more

Main survey

* 6. Have you read or heard about the use of cannabinoids for treatment of epilepsy in children?

Yes

No

7. Which component of cannabinoids is suggested to be most important for anti-epileptic activity

THC

CBD

THC and CBD

Do not know

* 8. Have you personally prescribed cannabinoids for treatment of children with epilepsy?

Yes

No

9. If you have not prescribed cannabinoids for epilepsy therapy in children - what are the reasons?

- No licenced product available
- Law regulations prohibiting the use of cannabinoid (off-label)
- Skepticism towards efficacy of this therapy
- Lack of knowledge/experience with this therapy
- I have prescribed cannabinoids for treatment of epilepsy
- Other (please specify)

10. If you have prescribed cannabinoids for treatment of children with epilepsy - which product did you use?

11. If you have prescribed cannabinoids for epilepsy therapy in children - which patients did you treat?

- Dravet syndrome (DS)
- Lennox-Gastaut syndrome (LGS)
- Infantile spasms (IS)
- Tuberous sclerosis complex (TSC)
- Other severe early-onset treatment-resistant epilepsies

12. If you have prescribed cannabinoids for epilepsy therapy in children - what is your impression of clinical efficacy?

- Moderate seizure burden reduction (> 50%)
- Good seizure burden reduction (> 90%)
- Shortening of seizures
- Less severe seizures
- Better life quality
- Improvement of cognitive ability
- No obvious effects

13. If you have prescribed cannabinoids for epilepsy therapy in children - which side effects did you experience or observe?

- Lethargy and drowsiness
- Gastrointestinal symptoms e.g. diarrhoea and vomiting
- Increased convulsions
- Fever
- Decreased appetite
- Other (please specify)

14. Has any of your patients or their relatives requested cannabinoid therapy for epilepsy?

- Yes
- No

15. Are you aware of cannabinoid self-medication (not prescribed by a doctor) among your patients with epilepsy?

- No
- Yes, 1-2 patients
- Yes, 3-4 patients
- Yes, at least 5 patients

16. Have you prescribed cannabinoid therapy to children/adolescents for any other indications than epilepsy?

- Yes
- No
- If yes, please describe shortly

Thank you for participating in this survey!

11. Summary of study design quality of the main articles from the bibliography

Reference: Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. New England Journal of Medicine. 2017;376(21):2011-20.		GRADE	
		Class of Evidence (CoE)	II
		Recommendation	B
Purpose	Material and method	Results	Discussion/commentaries
The trial consisted of one group that was treated with adjunctive cannabidiol versus one placebo group.	Study sign: The study was a multinational, randomized, double-blinded phase III trial. Inclusion criteria: The population were young adults 2-18 years old that had Dravet syndrome with seizures that were not under control by their current antiepileptic drug regimen Exclusion criteria: Clinically significant unstable medical conditions other than epilepsy. Past recreational or medical cannabis use. Randomization process: The randomization process is not revealed in the paper, but it is explained in the appendix protocol. An independent statistician produced randomization schedules, that were not divulged before unblinding. Blinding: The CBD solution and placebo solution were identical to the cannabidiol solution excepts for the absence of CBD. Data base: 120 underwent randomization. The characteristics of the trial groups were similar at baseline of the study. The placebo solution was identical to the CBD solution except for the absence of CBD. They were treated in and had the same routine protocols. In a figure it is presented that 9 patients in the CBD-group and 3 in the placebo group. The reasons of withdrawal are described. Out of the 108 patients who completed the study 108 entered an open-label study.	Primary and secondary endpoints were identified. Primary results: The results of the primary efficacy endpoint were presented like difference in percentage of the median number of convulsive seizures per month. The adjusted median difference in convulsive seizures between the CBD group and the placebo group was -22,8 percentage points (95% [CI], -41,1 to -5,4; P=0,01). Secondary results: When continued onward to secondary endpoints the reduction in convulsive-seizure frequency by 50 % or more during the treatment period occurred in 43% of the patients in the cannabidiol group and in 27 % of the patients in the placebo group (odds ratio 2.00; 95% [CI], 0,93 to 4.30; P=0,08). During the treatment period 3 patients in the cannabidiol group and no patients in the placebo group were free of seizures (P=0,08). All the endpoints were measured and presented. The results are representative and applicable in clinical situations if you consider the population.	It was approved by the review board or ethics committee at each participating institution and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Adverse effect where more prominent in the CBD group compared with the placebo (93% vs. 75% of the patients). Among patients with adverse events, 89 % had events that were mild or moderate in severity (84% in the CBD group and 95 % in the placebo group). There were however some serious adverse events (10 patients in the cannabidiol group and 3 in the placebo group). SE was reported in 3 patients in each group. Elevated levels of liver aminotransferase enzymes led to the withdrawal from the trial for 3 patients in the CBD group and 1 in the placebo group. All these patients were taking some form of valproate. As for limitations of the study, the founding source of the trial, GW Pharmaceuticals, was responsible for the trial design, (with input from investigators and other experts) trial management, site monitoring, trial pharmacovigilance, data analysis, and statistical analysis. GW Pharmaceuticals prepared and provided the active treatment and placebo. Another potential limitation to this partially subjective endpoint of convulsive-seizures frequency reported by caregivers is that the side effects of the drug being tested might unblind patients or caregivers to the trial-group assignments.
Conclusion	This RCT showed that CBD treatment in drug-resistant Dravet Patients, resulted in a greater reduction than placebo. Additional data are needed to determine the long-term efficacy and safety of cannabidiol .		
Country	23 centres in the U.S. and Europe		
Year of data collection	2015-2016		

Confounders:

CBD interactions with other AEDs.

Statistic methods:

A Wilcox rank-sum test is used to analyse the primary endpoint. An estimate of the median difference between CBD and Placebo was calculated with the Hodges-Lehmann approach.

Reference: Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085-96.		GRADE	
		Class of Evidence (CoE)	II
		Recommendation	B
Purpose	Material and method	Results	Discussion/commentaries
Assessing the efficacy and safety of CBD as an add-on anticonvulsant therapy in Lennox-Gastaut syndrome population. Additional data is needed to determine long-term efficacy, dosage issue and safety of CBD.	<p>Study sign: This study is a randomised, double-blinded, placebo controlled, phase III</p> <p>Inclusion criteria: Eligible patients were aged between 2 and 55 years, with a defined clinical diagnosis of Lennox-Gastaut.</p> <p>Exclusion criteria: Patients with clinically unstable illness (other than epilepsy), history of alcohol or substance abuse, recreational or medical cannabis users or had taken corticotrophins in the previous 6 months.</p> <p>Randomization: The randomisation schedule was produced by an independent statistician.</p> <p>Blinding: All patients, caregivers, investigators, and individuals assessing data were masked to group assignment. Both cannabidiol and placebo were provided in identical 100 mL amber glass bottles and could not be distinguished visually.</p> <p>Data base: The two treatment groups had similar patient demographics and baseline characteristics.</p> <p>171 were randomized (86 = CBD group and 85 = placebo group).</p> <p>Confounders: Drug-drug interactions between CBD and other AEDs. Hard to differentiate how much of the anti-convulsive effect is primarily from CBD.</p> <p>Statistic methods: The primary endpoint was assessed with a Wilcoxon rank-sum test, and the estimated median difference (with 95% CI) between the</p>	<p>Primary results: The primary endpoint was the percentage change in monthly frequency of drop seizures from baseline, measured during the 14-week treatment period.</p> <p>The estimated median difference between the treatment groups was -17,21 (95% CI – 30,32 to –4,09; p=0,0135) during the 14-week treatment period and –19,45 (-33,05 to –4,68; p=0,0096) during the 12-week maintenance period alone. Since the primary endpoint reached statistical significance, formal statistical analysis of the key secondary endpoints was permitted.</p> <p>Secondary results: The key secondary endpoints were the proportion of patients in each treatment group that achieved a reduction of 50% or more in monthly frequency of drop seizures.</p> <p>3 patients who were in the cannabidiol group and completed treatment were drop seizure free throughout the 12-week maintenance period. No patients in the placebo group were free of drop seizures. Also, the total amount of seizures in the cannabidiol group decreased more in comparison with the placebo group. The estimated median difference was –21,1 (95 % [CI] –33,3 to –9,4; p = 0,0005) during the treatment period and –23,3 (95% [CI] –36,3 to –10,5; p = 0,0004) during the 12-week maintenance period.</p> <p>Caregivers Global Impression of Change (GIC) in seizure duration, and change in sleep disruption and daytime sleepiness, quality of life, and adaptive behaviours.</p> <p>There were 3 times as many patients/caregivers in the cannabidiol group than the placebo group reporting their overall condition as very much improved (15 [18%] patients vs 5[6%] with the GIC-scale.</p>	<p>The study protocol was developed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines and approved by the institutional review board or independent ethics committee for each study site.</p> <p>Patients or caregivers recorded the number and type of seizures, including drop seizures, each day using an Interactive Voice Response System (IVRS). Patients or caregivers recorded information on study drug use, concomitant medications, and adverse events in a paper diary. Patients who completed treatment were eligible to enrol in an open-label extension trial.</p> <p>Common adverse effects (that occurred in more than 10 % of patients) in the cannabidiol group were diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. Of the patients who had all cause adverse events, the events resolved by the end of the trial in 45 (61%) patients in the cannabidiol group and 38 (64%) patients in the placebo group.</p> <p>There are some limitations of this study, the funding of the study came from GW pharmaceuticals.</p> <p>There are unmistakably drug-drug interactions and the potential of CBD and Valproate and Clobazam should be additional investigated.</p> <p>The use of subjective scales (GIC).</p> <p>The population of the trial (90% Caucasian) also makes it non-representative for other ethnicities.</p>
Conclusion	In this RCT with Lennox-Gastaut syndrome patients treated with CBD there was a significant reduction in frequency of drop, non-drop and total seizures.		
Country	The trial took place at 24 clinical sites in the USA (n=17), the Netherlands (n=1), and Poland (n=6).		
Year of dacolleciton	2015		

	<p>cannabidiol and placebo groups was compared using the Hodges-Lehmann method.</p> <p>According to the statistical analysis plan, if the primary endpoint was met (i.e., statistical significance was reached), the key secondary endpoints were to be tested in a hierarchical order.</p>		
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Reference: 1. Hess EJ, Moody KA, Geoffrey AL, Pollack SF, Skirvin LA, Bruno PL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. <i>Epilepsia</i> . 2016;57(10):1617-24.		GRADE	
		Class of Evidence (CoE)	III
		Recommendation	C
Purpose	Material and method	Results	Discussion/commentaries
To evaluate efficacy, safety and tolerability of CBD, as an adjunct to current AEDs in patients with refractory seizures in the setting of Tuberous sclerosis complex syndrome.	<p>Study sign: This was a prospective cohort study</p> <p>Inclusion criteria: To be eligible for the study a diagnosis of TSC (Tuberous sclerosis complex) was required, as well as treatment-resistant epilepsy, using between 1-7 AEDs at stable doses for a minimum of 2 weeks, stable vagus nerve stimulation settings, and stable ratios for ketogenic diet of minimum 4 weeks.</p> <p>Exclusion criteria: Allergies to ingredients in the study drug solution, use of cannabinoid therapy within 4 weeks before start of study, pregnancy, unstable hepatic, hematologic, renal, cardiovascular, gastrointestinal or pulmonary disease</p> <p>Data base: There were 18 patients that enrolled with TSC. 9 of the 18 TSC patients were male and so the other 9 females.</p> <p>The age range between 2-31 with an average of 14 years. 10 (55%) of the 18 patients underwent neuro-psychological testing, of whom 6 (60%) were cognitively impaired (IQ < 70).</p> <p>The median total weekly seizure frequency during the 4-week baseline period was 22 (IQR 14,8-57,4).</p> <p>Confounders: Drug-drug interactions occurred but were handled with reduction in dosing of AEDs.</p> <p>Statistic methods: Using a percentage change in seizure frequency at each time point, (2nd, 3rd, 6th, 9th, and 12th month), patients were defined as responders if they had a > 50% reduction in total seizure frequency.</p>	<p>Primary results: The median total weekly seizure frequency decreased to 14,9 (IQR 5,7-22,0) after 2 months treatment, 13,2 (IQR 5,06-22,1) after 3 months of treatment, 9,7 after 6 months and 7,7 after 9 months and 8,0 after 12 months of treatment</p> <p>Secondary results: After 3 months of treatment with CBD, four patients had a percent decrease in seizures of >80 %, and 2 patients had a decrease greater than 90 %. After 3 months of treatment with CBS, the median weekly seizure frequency decreased for all seizure types experienced by patients in the study. Based on calculated median percent changes in seizure frequencies after 3 months the greatest reduction in seizures was observed in tonic-clonic seizures (-91,4 %), followed by epileptic spasms (-87,5%), atonic seizures (-86,5%), complex partial seizures (-59,3%), tonic seizures (-48,2%) and complex partial seizures with secondary generalization (-38,6%).</p> <p>Comment: Patients who exited the study before a certain time point or patients who lacked follow-up to a given time point were not included in any calculations for the corresponding month.</p>	<p>The patients consented to the IRB (institutional review board) and FDA approved expanded-access study of CBD under Investigational New Drug (IND).</p> <p>12/18 patients in this study experienced at least one adverse event thought possibly could be related to CBD. Most adverse events experienced in this study were temporary and of mild severity. Adverse events were resolved through dose adjustments of CBD or concomitant antiepileptic drugs.</p> <p>At each clinic visit, patients or parents returned logs of recorded seizures since the last clinical visit. Changes in the dose of concomitant AEDs were made as clinically indicated. After third month of CBD treatment, doses of CBD and concomitant AED were changed monthly in nearly all patients in order to optimize seizure control.</p> <p>Limitations for this study is that it did not include a control group and was of small size. Then there is also the question of subjectivity in the reporting of seizures and how accurate those are.</p>
Conclusion			
In this study many patients with TSC exhibited an appreciable reduction in seizure frequency, with CBD as an add-on to their treatment regime.			
Country			
U.S.			
Year of data collection			
2014-2015			

Reference: Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.[Erratum appears in Lancet Neurol. 2016 Apr;15(4):352; PMID: 27302053]. Lancet Neurology. 2016;15(3):270-8.		GRADE	
		Class of Evidence (CoE)	III
		Recommendation	B
Purpose	Material and method	Results	Discussion/commentaries
To establish whether addition of CBD to existing anti-epileptic regimens would be safe, tolerated and efficacious in children and young adults with treatment-resistant epilepsy.	<p>Study sign: Prospective cohort/expanded-access open label trial.</p> <p>Inclusion criteria: Patients that had severe, childhood-onset and treatment-resistant epilepsy and had four or more countable seizures with a motor component per month and received stable doses of AEDs at least 4 weeks before enrolment.</p> <p>Exclusion criteria: Patients undergoing ketogenic or modified Atkins diet, had to have the ratio of fat to carbohydrate and protein stable for 4 weeks before enrolment. Similarly, individuals with a vagus nerve stimulation, settings had to be stable for minimum 4 weeks. Study-wide exclusion criteria included previous or current treatment with cannabis-based therapy.</p> <p>Data base: Patients at all sites were 1-30 years of age. The most common epilepsy syndromes treated were Dravet syndrome and Lennox-Gastaut syndrome. 214 patients were enrolled.</p> <p>Confounders:</p> <p>Statistic methods: Mann-Whitey-U test. Multiple logistic regression analysis. Analyses with IBM SPSS.</p> <p>Founding: GW Pharmaceuticals who also provided the treatment product had no role in study design, data analysis, data interpretation, or writing of the report.</p>	<p>162 patients (76%) had at least 12 weeks of follow-up after the first dose of cannabidiol.</p> <p>The primary endpoint was to establish the safety and tolerability of cannabidiol, and the primary efficacy outcome was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. For the second efficacy analysis the median percentage change in other seizure types, including tonic, atonic, tonic-clonic, focal non-motor, and total seizures was assessed.</p> <p>Primary results: The median change in total seizures was –34,6% (IQR –66,7 to –9,8), with the greatest reduction occurring in patients with focal seizures or atonic seizures, followed by tonic seizures or tonic-clonic seizures.</p> <p>Secondary results: Analysis of the secondary endpoints of responder rates showed that 54 (39%) patients had a reduction of 50% or more motor seizures, whereas 29 (21%) had a reduction of 70% or more and 12 (9%) had a reduction of 90% or more. Two patients were free of all seizure types over the entire 12 weeks. All results are well presented.</p>	<p>Because each of the 11 study sites applied for their own investigational new drug registration for the expanded-access programme, there was some variability in eligibility criteria between centres.</p> <p>All seizures were recorded by parents or caregivers on paper diaries and reviewed by the study team at each clinical visit. Tolerability and adverse effects were assessed every 2 weeks by use of the Liverpool Adverse Events Profile or the Paediatric Epilepsy Side Effects Questionnaire, depending on age.</p> <p>Reasons for withdrawal included allergy to the sesame oil vehicle, hepatotoxicity, excessive somnolence and poor efficacy, gastrointestinal intolerance, worsening seizures, and hyperammonaemia</p> <p>Most adverse events were mild or moderate and transient. Serious adverse events were reported in 48 (30 %) patients. Serious adverse events deemed possibly related to cannabidiol use were recorded in 20 patients and included status epilepticus, diarrhoea, pneumonia, and weight loss. 11 (7%) patients had elevated liver function tests, one patient had a significant increase in transaminases leading to discontinuation of cannabidiol. The adverse event profile of cannabidiol was favourable, with most patients tolerating the drug well despite its addition to a median of three concomitant antiepileptic drugs</p> <p>The major limitations of this story were that it was open label and uncontrolled. The issue of the placebo response is especially relevant in paediatric trials of cannabis-derived treatments. Among findings from 32 randomised controlled trials of add-on treatment in patients with epilepsy, children had a significantly higher response to placebo (19%) than adults, whereas responder rates to the trial intervention were similar. A placebo effect is also more concerning with cannabis-based preparations than with other antiepileptic drugs because of the intense media and family interest in the compound.</p>
Conclusion			
The safety and tolerability was acceptable, with only five (3%) out of 162 patients stopping treatment because of adverse effects. The efficacy seems promising, however RCTs are needed to characterise the safety profile and true efficacy.			
Country			
11 epilepsy centres across the USA			
Year of data collection			
Jan. 2014 – Jan. 2015			

Reference: Treat L, Chapman KE, Colborn KL, Knupp KG. Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients. Epilepsia. 2017;58(1):123-7.		GRADE	
		Class of Evidence (CoE)	III
		Recommendation	C
Purpose	Material and method	Results	Discussion/commentaries
<p>The purpose of this study was to measure the duration of use and perceived efficacy of Oral Cannabis Extracts (OCEs) in a cohort of patients with paediatric epilepsy.</p>	<p>Study sign: Retrospective cohort, medical chart review.</p> <p>Inclusion criteria: Patients were included in this study if they carried a diagnosis of epilepsy and had a documented seizure frequency, both before and after initiation of OCEs. The participants included were from 30 days to 18 years of age.</p> <p>Exclusion criteria: Nondaily use of OCEs, or if OCEs were used for reasons other than seizure control.</p> <p>Data base: Sample size 119.</p> <p>Confounders: Bias of patients that had relocated til Colorado seemed to overreport efficacy of treatment</p> <p>Statistic methods: Multiple Cox proportional hazard (PH) model, Fisher's exact test,</p>	<p>Epilepsy syndrome and seizures types were recorded as documented by the treating clinician, according to the ILAE classification.</p> <p>Seizure response was based on a parental report of seizure frequency prior to initiating ICEs compared to the last documentation of seizure frequency while on OCEs.</p> <p>Patients were considered responders to OCEs if parents reported a > 50 % reduction in seizure frequency.</p> <p>Primary results: The parents of 58 patients (49%) reported at least some improvement in seizures. 24% of the cohort were considered to be responders to OCE treatment.</p> <p>Secondary results: Lennox-Gastaut syndrome (LGS) was the only syndrome type associated with a significantly higher proportion of responders when compared to all other patients in the cohort: 11 (58%) of 19 patients (p < 0.05).</p> <p>Perception of any seizure benefit was the only factor significantly associated with longer duration of OCE use (p <0,01).</p> <p>Only Dravet syndrome emerged as significantly impacting duration of OCE use, and the presence of this diagnosis was associated with a shorter duration (p = 0.02)</p> <p>Relocation to Colorado was associated with perceived benefit of OCEs (65% vs 38% p=0,01), but was not independently associated with longer use of OCEs.</p> <p>Non-seizure benefits were also reported, including improved behaviour/alertness in 46 patients (39%), improved motor skills in 9 (8%), and better sleep in 8 (7%).</p>	<p>Of the 119 patients included, 41% had relocated with their families to Colorado prior to starting OCEs. Patients were considered to have moved to Colorado for OCEs if evidence of this relocation was documented in the electronic record.</p> <p>An interaction between relocation to Colorado and perception of seizure benefit was not significant, so it was excluded from the multiple Cox PH model.</p> <p>The most common AEs included worsening of seizures in 10 patients (8%), somnolence in 7 (6%), and gastrointestinal symptoms in 6 (5%). Eighty-four patients (71%) discontinued their OCE use during the study period.</p> <p>What is seen in the study is that parental perception of benefit of OCEs on seizure profile is a key driver of continued use of OCEs. The relocation to Colorado for usage of OCEs has been shown to predict parental perception of benefit. This suggest that sociologic factors may also play a role in medical decision making about OCEs.</p> <p>There are limitations to this study, like the recall bias on behalf of the parental report. The alterations of prescribed AEDs. The non-discrimination of different OCEs The available information on the retrospective chart, might differ in consistency in documentation.</p>
Conclusion			
<p>Duration of OCEs have some predictable patterns. Parental perception of benefit is a key driver of continued OCEs, Remarkably, at least one third of patients who did not experience any seizure benefit continued to use OCEs at last follow-up, which could reflect use of the product for a non-seizure benefit.</p>			
Country			
USA			
Year of data collection			
2013- 2015			