

Case Study Report – Subject 2

Cannabidiol Oil trial in Adult Male with Uncontrolled Epilepsy, Complex Post Traumatic Stress Disorder and Pain

Introduction

Cannabidiol/CBD has recently come to prominence in the media as a treatment for a variety of ailments, ranging from reduction of simple mechanical pain e.g. knocks and bruises, to a cure for cancer. It is a derivative of the hemp/cannabis plant, without the active ingredient (tetrahydrocannabinol/THC) that induces the cannabis “high” (Wray et al., 2017). There is a plethora of anecdotal “evidence” to be found on the internet, with the suggestion that it can help almost any condition, including epilepsy, musculoskeletal pain, and Post Traumatic Stress Disorder (PTSD). It is available in a wide range of strengths and qualities, from back street herbalists to medical grade suppliers (Halperin, 2018).

Epilepsy is a condition typified by so called electrical storms or seizures in the brain. Causality varies. There may be a genetic cause in some people, but genetic testing isn’t yet available for many types of epilepsy. About 30% of epilepsy is caused by a change in the structure of the brain. Brain infections can leave scarring on the brain that can cause epilepsy onset at a later stage. Head injuries can also lead to epilepsy, and later in life, strokes and tumours may be the cause, as can Alzheimer’s disease and other neurological conditions (Schacter et al., 2013)

The research done and published to date with cannabinoids documents some positive outcomes in research and treatment of mostly childhood epilepsy, central nervous system problems and psychotic disorders, although much of it is based on self-reporting by users/parents of children with epilepsy (Devinsky et al., 2016; Porter and Jacobsen, 2013; Palmieri et al., 2017).

Latterly, as interest has risen in self-reported improvements and anecdotal evidence, research has progressed to more robust controlled trials (Devinsky, Patel et al., 2018). There continue to be interesting studies in animals *for example* research on CBD in mice relating to Huntington’s Disease (Consroe et al., 1991; Valdeolivas et al., 2015) but these cannot yet be extrapolated to the human population.

It is known, following extensive research into the properties of cannabis and related products, which includes CBD oil, that the body has 2 types of cannabinoid receptors which are distributed throughout the central nervous system (CNS) (Rosenberg et al., 2015). These receptors have an important role in the control of transmission across synapses and the regulation of neural firing (Mechoulam and Parker).

A study found that anandamide, an endogenous substance which interacts with cannabinoid receptors (Di Marzo et al., 2002), was reduced in adults with recently diagnosed temporal lobe epilepsy (Romigi et al., 2010). CBD has been shown to stop electrically induced seizures in mice (Consroe et al., 1991).

A 2017 trial with cannabinoids in childhood epilepsy which was randomised, controlled and double blinded, showed a reduction in seizures with a significance of +50 (Devinsky et al., 2017) but a critic of the trial (Peruca 2017), says that this may be more due to CBD and drug interaction with clobazam which the patients were already taking.

In epilepsy, there is some evidence that CBD administration can interact with clobazam, causing drowsiness, therefore adding a caution to patients already taking this drug for their epilepsy. However, the increased drowsiness experienced was eliminated by reducing the clobazam dosage (Geffrey et al., 2015). The only other adverse effects of CBD have been elevation in liver enzymes, much more frequently with those taking sodium valproate, but these levels returned to normal after a few weeks of using CBD products (Devinsky et al., 2016 Devinsky et al., 2017; Thiele et al., 2018).

Post-traumatic stress disorder (PTSD) is a psychological condition caused by witnessing or being involved in traumatic events eg physical/sexual assault, military combat, natural disasters (www.nhs.uk 2015; Bailey et al., 2013).

It is typified by symptoms which last for over a month after the event (Bailey et al., 2013), with reliving of traumatic memories through flashbacks or nightmares, sometimes with feelings of isolation, guilt and irritability, insomnia, and concentration problems (www.nhs.uk) avoidance and numbing, alteration in physical and emotional reactions and hypervigilance (Mayo Clinic 2018) (Nebraska Department of Veterans Affairs, 2007).

PTSD is prevalent in the US population, at approximately 8-14% (Davison et al., 1991. Kessler et al., 1995. Breslau et al., 1998), with twice as many cases in females compared with males (Breslau et al., 1998. Resnick et al., 1993). This author was unable to find comparative data for the UK.

Complex PTSD is more likely to be diagnosed in adults and children who had traumatic experiences in early childhood e.g. violence, abuse or neglect; whose trauma went on over a period of time; whose abuse was caused by a parent or carer; who still have contact with their abuser/s; who were isolated during the trauma (www.nhs.uk). In adults it can occur as a result of prolonged trauma e.g. kidnap or torture scenarios. It can take years for the symptoms of complex PTSD to be recognised, and a child's development can be altered. The earlier the age, the worse the trauma. (Royal College of Psychiatry 2015).

Pharmacological treatment is based on selective serotonin reuptake inhibitors (SRRIs) or selective noradrenaline (norepinephrine) combined with cognitive behavioural therapy, (Benedek 2009) but response rates are low, with only 20-30% clinical remission, and poor comparison to placebo in trials Davidson 2006. Friedman et al., 2007).

Medication in PTSD has been largely based on observation of drugs approved for other conditions, (no drug has been developed specifically for treatment of PTSD) and there are limited effective treatment options in chronic PTSD (Papini et al., 2015).

The cannabinoid receptor system, along with other receptors, has been shown to play a crucial role in fear patterns (Ruehle et al., 2012). A study where PTSD symptoms were induced in mice by scaring them with a cat showed a reduction in histological changes at the hippocampus and frontal cortex following use of CBD (Campos AC et al., 2012). A gender difference has also been shown in animals (Reich et al., 2009. Suarez et al., 2009) supporting the figures for higher incidence of PTSD in human females (Galovski et al., 2013, McGregor et al., 2017).

Papini et al., 2015 stated that a review of current research done in humans with PTSD using CBD showed inconsistent results. Shannon et al., (2016) cite a case of successful outcomes with cannabidiol oil for a child with PTSD.

Blessing et al., 2015 state that the evidence from preclinical and human experimental trials reviewed by them 'strongly supports CBD as a treatment for generalized anxiety disorder,

panic disorder, social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing.' They suggest the need for more study, particularly of chronic PTSD cases.

Pain is described as an “unpleasant feeling that is conveyed to the brain by nerves in the body” (Health of Children 2018) which can arise from multiple causes such as injury, illness, or as a co-symptom with a psychological condition, or from no known cause.

Pain sensation is used to signal potential or actual damage to the body, by triggering protective responses, but it may cease to be simply a warning system and become chronic and debilitating instead (Julius and Basbaum 2008).

According to McCaffrey (1999), quoted in Pasero, 2009, “Pain is what the experiencing person says it is, existing whenever he says it does”. A web article aimed at medical students (Symptoms and Descriptions of Pain, 2018) states that the commonest descriptors of pain level are mild, bad, severe, violent and excruciating. These are then given other descriptors to explain the sensation for example stabbing, cutting, stinging, burning, boring, splitting, colicky, crushing, gnawing, nagging, gripping, scalding, shooting, throbbing, cramping, radiating, dull, sharp, localized, general, persistent, recurrent, chronic. Patients may complain of insomnia, dizziness, nausea, anorexia or heartburn, restlessness and fatigue (Symptoms and Descriptions of Pain, 2018).

Russo (2004) suggested that endocannabinoid deficiency may be a factor in some treatment-resistant pain subjects and conditions, supported by research by Sarchielli et al (2006) which found a decrease in anandamide levels in patients with migraine.

Cannabinoid receptors CB₁ (Howlett et al 1988) and CB₂ (Munro et al 1993) are distributed widely throughout the body, but the CB₁ receptor is present in more areas, especially in the nociceptive areas in the central (Herkenham et al 1990; Hohmann et al 1999) and peripheral nervous systems (Fox et al 2001; Dogrul et al 2003). There is a direct link between the action of the CNS and peripheral nervous system receptors (Dogrul et al 2003).

Cannabinoids are 10-fold more efficient in thalamic pain mediation than morphine receptors (Martin et al 1996). Experiments in mice suggest that peripheral CB₁ nociceptors are more important in pain perception than central ones (Agarwal et al 2007) and stimulation of CB₁ receptors decreases pain, hyperalgesia and inflammation.

CBD also promotes signalling of the A2A adenosine receptor which may additionally explain its inflammatory and analgesic effects (Carrier et al 2006). Malfait et al (2000) demonstrated inhibition of the TNF- α tumour necrosis factor in rodent models of rheumatoid arthritis by CBD.

CBD Blocks hyperalgesia in substance P mechanisms (Li et al 1999), and by inhibiting calcitonin gene-related peptide (Richardson et al 1998). It also has a higher anti-oxidant function than vitamins C and E (Hampson et al 1998). CBD has been recognised as the first clinically available endocannabinoid modulator (Russo and Guy 2006).

Trials done in Canada with Sativex[®] (GW Pharmaceuticals) , a whole cannabis spray for oromucosal use (Russo and Guy 2006) have shown that this product, compared with placebo and THC extract, gives significant improvements in opiate non-responsive pain in cancer subjects. The suggestion is that it is therefore the CBD component of Sativex[®] , rather than the THC component that is necessary for pain relief (Johnson and Potts 2005). Sleep patterns in chronic pain subjects have also improved with this product in nearly all

random controlled trials (Russo et al 2007). Treatment effects ceased after 7-10 days when medication with Sativex[®] was stopped, but symptom control was easy to re-establish by taking the medication again (Wade et al 2006).

General CBD information

CBD has an initial half-life of 6 hours, as it is digested, and then an additional 24-hour half-life as it is slowly distributed into tissues (Welty et al., 2014).

There is some evidence that CBD becomes more bio-available if ingested at the same time as food, but this was research done with a nasal spray also containing THC (Sativex[®]), approved in some countries for the reduction of spasticity in Multiple Sclerosis (Stott et al., 2013) so may not be relevant to oral administration (Peruca 2017).

Trial dosages have been from 10 mg per kilo to 20 mg CBD per kilo body weight, with adverse effects in the higher dosage groups, mostly somnolence and decreased appetite (Devinsky et al., 2017).

There is no evidence of withdrawal symptoms after medication with CBD (Devinsky et al., 2017). Treatment with NSAIDs for pain has been shown to increase likelihood of gastrointestinal ulcers and bleeding, myocardial infarction and strokes (Fitzgerald 2004; Topol 2004), but none of these increased risk factors has been found with CBD (Stott et al 2005).

Cannabinoids may offer significant “side benefits” beyond analgesia. These include anti-emetic effects, well established with THC, but additionally demonstrated for CBD (Pertwee 2005), the ability of THC and CBD to produce apoptosis in malignant cells and inhibit cancer-induced angiogenesis (Kogan 2005; Ligresti et al 2006), as well as the neuroprotective antioxidant properties of the two substances (Hampson et al 1998), and improvements in symptomatic insomnia (Russo et al 2007).

There are some concerns about quality control and variability of products available to the general public, as most adult patients self-medicate with CBD products (Peruca, 2017).

This author has been unable to find any published research available in adults for uncontrolled epilepsy. It was felt that case study research in CBD for adult uncontrolled epilepsy would add to the existing research base, whilst potentially helping this subject to get symptomatic relief. Research for PTSD and pain, as cited above, has been done mostly with THC containing compounds, so there is a case for more study with CBD oil only.

History

This case involves a 51-year old adult male who has had uncontrolled epilepsy since 2007, ongoing pain, and was diagnosed with PTSD in 2011.

The epilepsy worsened, and the PTSD symptoms started after a family tragedy in 2008, which also resulted in his recovery of memories of childhood abuse. He was subsequently diagnosed with complex Post Traumatic Stress Disorder (PTSD) and has been under the continuing care of the Community Psychiatric Nursing Department. He has made several attempts on his own life in the past few years.

His epilepsy has resulted in approximately 14 episodes of hospitalization in the past 12 months. His seizures come on suddenly, with no warning signs to him, although his wife

reports that she can see signs of an impending seizure, as he twitches and has a vacant stare.

During his seizures he usually falls to the floor and moves around a lot, which results in injuries caused by collisions with e.g. furniture. He therefore also has constant pain, which moves around relating to the injuries sustained in his latest epileptic episode. He has continuing shoulder and low back pain.

Medication consists of Keppra/levetiracetam 1500 mg x 2 twice daily; Epilim/sodium valproate twice daily, am 500mg, pm 2x 500mg; Gabarone /gabapentin 600 mg x 2 daily; Mirtazepine 45mg once daily.

He has been married for 27 years. He has his own vehicle windscreen replacement company, and voluntarily coaches children's football several nights per week and attends matches at the weekends.

It is postulated that increasing cannabinoids in this subject's system may help in reducing epileptic seizure activity, controlling PTSD symptoms, and reducing pain.

Tests And Measurements

Prior to the start of the trial, the subject was asked to keep a seizure diary, as supplied by the UK epilepsy society (Epilepsy Society 2016 smartphone app) to provide a baseline number of seizure episodes over a four-week period prior to the commencement of the trial. This showed fits from 12-17 times per week (mean average 14.5), with no warning that they were coming on. He had approximately 14 hospital admissions in the year prior to the trial.

The McGill Pain Questionnaire (Melzack 1975) was administered to establish pre-trial pain levels.

Self-reported moderate pain levels in multiple areas, as a result of falling to the floor and moving uncontrollably, often colliding with furniture etc. during his seizures.

A PTSD test (Weathers et al. 1994) was administered to establish pre-trial PTSD levels.

Self-reported PTSD symptoms were 'severe'.

Table 1 Pre-test scores

	Pre
PPI	6.00
NWC	16.00
PRI	33.93

Anxiety Screening	n/a
PTSD Screening	63.00
Change in Pain Levels	
Fit Frequency (per week)	12 to 17
Fit Frequency Change %	

PPI (Pain Perception Index) at 5, horrible, on the McGill Pain Questionnaire (Melzack 1975). This is the patient's perception of their pain level, with a choice of six options, ranging from 0 – none to 6 – excruciating

Number word count (NWC) 16 (Melzack 1975).

This is the number of descriptive words chosen for pain, from a possible maximum total of 78. The descriptive words are also in categories for sensory perception of pain, affective, emotional and miscellaneous. Higher numbers here indicate more perceived pain.

Pain score 33.93 on the McGill Pain Questionnaire (Melzack 1975).

This is the total score for all categories, from a possible maximum total of 214 with each word being multiplied by a ranking for each section. An example for this subject would be the word 'tiring' which has a ranking of 1 and a multiplier of 1.74, or 'hurting', which has a ranking of 3 and a multiplier of 0.72.

PTSD score of 63 on the PTSD Checklist (Weathers et al. 1994)

Treatment

The subject was supplied with an EVR 18% 10 ml airless metered pen and instructed to use it once daily for 6-8 weeks, and to take an additional dose if he knew that he was about to have a fit; or get another adult to administer it during fits.

Subjective reporting was that during the trial, there was a decrease in fits to 2-3 per week after the first 2 weeks, and his wife reported that the length and intensity of the fits was reduced. He was still unable to tell when a fit was about to come on, and his wife had been unable to administer doses during fits.

Results

PPI (Pain Perception Index) at 4, distressing, on the McGill Pain Questionnaire (Melzack 1975), which was a drop from 5 'horrible' to 4 'distressing', possibly indicating that he was managing his pain better emotionally.

Number word count (NWC) had increased from 16-20 (see possible explanation below). This is the number of descriptive words chosen for pain, from a possible maximum total of 78. The descriptive words are also in categories for sensory perception of pain, affective, emotional and miscellaneous. Higher numbers here indicate more perceived pain (Melzack 1975).

Pain levels had increased by -42.35% on the McGill Pain Questionnaire (Melzack 1975), which was considerably worse, but reporting was done after he had had a fit, when his pain tends to be worse, as he often injures himself during fits.

PTSD score dropped to 32 from 63 (Weathers et al. 1994).

This score is still indicative of PTSD, but it had much improved, particularly in the areas of flashbacks “*acting or feeling as if a stressful experience is happening again*”; triggers “*feeling very upset when something reminds you of a stressful situation*”; physical reactions “*heart pounding, trouble breathing, sweating when something reminds you of a stressful situation*”; sleep pattern “*ability to fall asleep and stay asleep*”, and catastrophic thinking “*feeling as if the future will be cut short*”. (Weathers et al. 1994)

There had been a mean average 82.76% decrease in fit frequency (from mean average 14.5 to mean average 2.5 seizures per week).

Subject reported that his epilepsy and PTSD symptoms had been enormously improved by the CBD oil.

Three weeks after the end of the trial, the subject is no longer using CBD products, and fits and PTSD symptoms have all returned to pre-trial levels. This subject wants to use a higher dose of CBD metered pen in the future to see if continued use will give even more symptomatic relief.

Table 2 Post-trial scores

	Pre	Post
PPI	6.00	4.00
NWC	16.00	20.00
PRI	33.93	48.30
Anxiety Screening	n/a	n/a
PTSD Screening	63.00	32.00
Change in Pain Levels		-42.35%
Fit Frequency (per week)	12 to 17	2 to 3
Fit Frequency Change %		82.76%

Discussion

The CBD product used by this subject was effective in decreasing epileptic seizure activity to a significant extent. It also decreased his PTSD symptoms markedly.

There is a possibility that taking a higher percentage CBD product for a longer period would stop seizure activity, and further reduce or stop PTSD symptoms.

Cessation of CBD treatment in this subject led to an almost immediate reversion to pre-trial seizure activity and PTSD symptoms, which suggests that CBD products need to be taken for longer, and possibly continued long-term for on-going symptomatic relief.

The exact dosages required to terminate seizure activity will probably differ from subject to subject. This study shows potentially very encouraging results for adults with uncontrolled epilepsy and for PTSD. Further research with double blinded and controlled trials and large patient numbers is suggested.

If a higher dose of CBD oil can be shown to reduce or stop seizure activity and PTSD symptoms completely, there is also scope for research into neuropathological activity changes at cannabinoid receptors after a course of CBD administration.

Author Notes

Jane S. Campbell BSc (Hons) qualified as an acupuncturist in 1985, added cranio-sacral therapy training to advanced level and subsequently did a BSc Professional Studies in Healthcare at Teesside University in 1992. She has private practices in Guisborough, North Yorkshire, UK, and in Rhodes, Greece.

These Case Studies are a result of being asked to provide CBD products for sale in the practices. This was not possible without knowing the possible benefits or side effects. Since there was little evidence other than anecdotal, or in children, or using products containing THC, the case studies were the only way to provide the information necessary to consider offering the products for eventual sale.

The samples used were provided free on request from EVR, with no expectation of reward, sales or endorsement.

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