Case Study Report 1

Cannabidiol Oil trial in Adult Female with Uncontrolled Epilepsy

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).

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 gastro-intestinal 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.

History

This case involves a 34-year old adult female who has had uncontrolled epilepsy since 2004. Her diagnoses varied for a few years, from epileptic to non-epileptic seizures and back again, with various differing medication regimes. She was finally diagnosed with “comorbid” epilepsy, a combination of frontal lobe, complex parietal lobe and non-epileptic seizures, in 2015.

Her epilepsy has resulted in at least 10 episodes of hospitalization in the past 12 months. Her seizures are of three different types, which she describes as: 1) complex, big/massive, usually falls to the floor and moves around a lot, with drooling and /or tongue bite. Followed by sleep for 20 minutes to 2 hours, with a big headache and aches in the right side of her body afterwards 2) Focal partial, not so big, less intense/shorter (sometimes) but otherwise similar to type 1). Sleeps for about 20 minutes afterwards 3) non-epileptic, absence, feels

disconnected. Followed by confusion, sometimes tiredness and slight headache, with some memory loss from seconds/minutes pre-seizure.

Medication consists of Keppra/levetiracetam 1500 mg twice daily, Lamotigrine 200mg twice daily, Lacosamide 150mg twice daily, fluoxetine 40mg once daily

She has been married for 10 years and has a four-year-old daughter.

It is postulated that increasing cannabinoids in this subject's system may help in reducing epileptic seizure activity.

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 and 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 1-6 times per week (mean average 3.5), with no warning that they were coming on. She was hospitalised 3 times in the 4 weeks prior to the trial.

Table 1 Pre-trial scores

	Pre
Fit Frequency (per week)	1 to 6
Fit Frequency Change %	

Treatment

The subject was supplied with an EVR 25% 10 ml airless metered pen and instructed to use it once daily for 6-8 weeks, and to take an additional dose if she knew that she 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 gradual decrease in fit frequency and episodes of hospitalisation. She was now able to tell when a lot of her fits were about to start and was able to self-medicate with an additional dose of CBD oil and prevent or curtail them. Her husband had been unable to administer doses during fits.

Results

There had been a mean average 100% decrease in fit frequency (from mean average 3.5 to mean average 0 seizures per week). She was hospitalised only once in the final four weeks of the trial.

Subject reported she was unwilling to stop using CBD products as she felt so much improved, so kept the remains of the contents of the metered pen to use in case she could feel a seizure coming on and bought some low percentage (un-stated) CBD oil from a local shop to take twice daily. Four weeks post trial, she has had only one seizure, but it was a severe one and she was hospitalised. She puts this down to over-heating whilst on holiday.

Table 2 Post-trial scores

	Pre	**Post**

Fit Frequency (per week)	1 to 6	0
Fit Frequency Change %		100.00%

Discussion

There can be no doubt that the CBD product used by this subject was exceptionally effective in decreasing epileptic and non-epileptic seizure activity, as she had a 100% reduction in seizure activity.

There would appear to be a benefit in taking a higher percentage CBD product for several weeks, and then moving to a lower 'maintenance dose'.

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

Author Notes

Jane Sutton BSc (Hons) MCSP Grad Dip Phys MAACP qualified as a physiotherapist in 1983. She has private physiotherapy 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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Ends …

Case Study Report 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).

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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.

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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 (norephinephrine) 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 CB_1 (Howlett et al 1988)and CB_2 (Munro et al 1993) are distributed widely throughout the body, but the CB_1 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 CB_1 nociceptors are more important in pain perception than central ones (Agarwal et al 2007) and stimulation of CB_1 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 gastro-intestinal 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 Sutton BSc (Hons) MCSP Grad Dip Phys MAACP qualified as a physiotherapist in 1983. She has private physiotherapy 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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Ends …

Case Study Report 3

Cannabidiol Oil trial in Adult Female with 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).

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).

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).

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.

Pharmacological treatment is based on selective serotonin reuptake inhibitors (SRRIs) or selective noradrenaline (norephinephrine) 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 CB_1 (Howlett et al. 1988)and CB_2 (Munro et al., 1993) are distributed widely throughout the body, but the CB_1 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 CB_1 nociceptors are more important in pain perception than central ones (Agarwal et al., 2007) and stimulation of CB_1 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 gastro-intestinal 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).

Research for PTSD and pain, as cited above, has been done mostly with THC containing compounds, so it was felt that case study research with CBD oil may add to the existing knowledge base.

History

This case involves a 56-year old adult female who was diagnosed with complex PTSD in 2000, and has ongoing pain following a car crash in 2010.

The PTSD symptoms started after recovery of memories of childhood abuse. She was diagnosed with complex Post Traumatic Stress Disorder (PTSD) and subsequently with Disassociative Identity Disorder (DID) in 2016 and has been under the continuing care of her GP for medication. She has had multiple interactions with counselling services since initial diagnosis of PTSD in 2000.

Unremitting pain began following a car accident, where the car rolled over several times following a skid in ice/snow. Because of her history of PTSD, she has poor self-care strategies, and failed to seek appropriate treatment until 2017, when she began a weekly course of physiotherapy because the pain was increasing, spreading to other structures and limiting her capacities. She reports a decrease in pain of about 25% of previous following this treatment, which stopped a few weeks prior to the CBD trial. She has problems with her left foot, including 'giving way, suddenly, pain in certain prolonged positions ie high heels, and reduced balance. She has right pelvic pain, right thoracic pain with nerve involvement, almost constant head and neck pain, low back pain and bilateral leg pain with regular cramp.

Medication consists of venlafaxine 50mg x 1 daily for the PTSD and regular self-medication with ibuprofen and paracetomol PRN for pain.

She is in the middle of divorce proceedings from her marriage in 2013 and has been living with her current partner for a year. She runs two businesses and travels abroad extensively for work.

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

Tests And Measurements

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

Self-reported pain in multiple areas: left foot, constant head, cervical, thoracic and leg pain with cramp, and regular low back pain.

A PTSD test (Weathers et al., 1994) was administered to establish pre-trial PTSD levels. Self-reported pain in multiple areas: left foot, constant head, cervical, thoracic and leg pain with cramp, and regular low back pain.

Self-reported PTSD symptoms were 'moderate'.

Table 1 Pre-trial scores

	Pre
PPI	3.00
NWC	15.00
PRI	32.54
Anxiety Screening	n/a
PTSD Screening	66.00

Change in Pain Levels	

Pain Perception Index (PPI) at 3, discomforting, on the McGill Pain Questionnaire. This is the patient's perception of their pain level, with a choice of six options, ranging from 0 – none to 6 – excruciating (Melzack 1975).

Number word count (NWC) 15.
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 score 32.54 on the McGill Pain Questionnaire. 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 (Melzack 1975).

PTSD score of 66 on the PTSD Checklist (Weathers et al., 1994).

Treatment

The subject was supplied with an EVR 22% 10 ml airless metered pen and instructed to use it once daily for 6-8 weeks, and a jar of EVR Premium Hemp Oil CBD Salve to use topically at pain sites.

Subjective reporting was an admission to only using the pen when the pain was bad enough to remind her to do something, rather than taking it daily as instructed. She used the topical salve and reported that it gave good relief of pain when applied.

Results

PPI remained the same, at 3, 'discomforting', on the McGill Pain Questionnaire possibly because of bilateral shoulder pain, which had not been present at the beginning of the trial. This is the patient's perception of their pain level, with a choice of six options, ranging from 0 – none to 6 – excruciating (Melzack 1975).

Number word count (NWC) had decreased from 15-13 possibly due to an alteration in the number and types of pain site.
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 reduced by 15.77% (non-significant) on the McGill Pain Questionnaire.
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 (Melzack 1975).

PTSD score (Weathers et al., 1994) had dropped to 44 from 66.

Score still indicative of PTSD presence, but there was a slight improvement in all areas, and improvement to non-symptomatic in the areas of "*loss of interest in previously enjoyed activities"* and *"feeling distant or cut off from other people"*.

Subject reported that nightmares were episodic during the trial, rather than every night but increased when stress levels were higher. "*Loss of interest in previously enjoyed activities"* stopped being an issue during the trial and had not returned by 3 weeks post trial, which had improved perceived quality of life.

Previous head pain had gone completely, previous right cervical pain was now occasional instead of continuous, low back pain was rare, leg pain had gone.

Regular cramp still present, thoracic pain unaltered and developed bilateral shoulder pain which hadn't been present previously. This was attributed to a huge increase in driving. The salve was effective in reducing this "by about 75%" when applied.

The subject reports that she felt that the products supplied to her for the trial had been partially effective, and she would use them again, and more regularly now that she had been reminded to use them daily, to see if all of her symptoms could be further improved.

A preference for an oral CBD product in tablet form was expressed due to disliking the taste of the oil.

Table 2 Post-trial scores

	Pre	Post
PPI	3.00	3.00
NWC	15.00	13.00
PRI	32.54	27.41
Anxiety Screening	n/a	n/a
PTSD Screening	66.00	44.00
Change in Pain Levels		15.77%

Discussion

This subject was non-compliant with the case study protocol in that she failed to take the CBD product supplied daily for the course of the trial period. This may be a continuing example of her poor self-care strategies, which cannot be examined in this study.

There was a statistically insignificant reduction in pain scores, although the latter may have been skewed by development of severe shoulder pain which had not been present previously and be affected by intermittent use of the product.

The study protocol was flawed in respect of the CBD topical product. There is no way to separate its potential effects from those of the oral product, and any results that may have been suggested can only be taken as anecdotal. Further double-blinded, controlled trials with large participant numbers are suggested to judge the efficacy of the topical product in isolation from the oral product.

Use of the products was intermittent throughout the trial however there was still a good reduction in the PTSD score, which is potentially very encouraging for other adults with this condition.

Further research is therefore suggested especially in the use of CBD products for PTSD.

Author Notes

Jane Sutton BSc (Hons) MCSP Grad Dip Phys MAACP qualified as a physiotherapist in 1983. She has private physiotherapy 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.

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Ends …

Case Study Report 4

Cannabidiol Oil Trial in Adult Male with Anylosing Spondylitis 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, musculo-skeletal 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).

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, 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 CB_1 (Howlett et al 1988)and CB_2 (Munro et al 1993) are distributed widely throughout the body, but the CB_1 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 CB_1 nociceptors are more important in pain perception than central ones (Agarwal et al 2007) and stimulation of CB_1 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 1998a). 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).

Ankylosing Spondylitis is an inflammatory disease which affects the skeleton. It is more prevalent in men than women (Mouyis and Keate, 2012) and onset is usually in young adults.

It is typified by low back pain and morning stiffness, which improves with movement or exercise. In most cases, symptoms gradually spread to the cervical and thoracic spine, and other joints may be involved eg hips and knees. Some cases develop a severe disease process with unremitting pain (McKenna 2010).

There is a genetic association with the HLA B27 antigen, though many people who have the antigen do not go on to develop the disease (McKenna 2010).

CBD research in ankylosing spondylitis per se is rare, but studies have shown beneficial anti-inflammatory effects of CBD and THC at cellular level via modulation of cytokenes (Nagarkatti et al., 2009).

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 gastro-intestinal 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).

Research in pain, as cited above, has been done mostly with THC containing compounds, so there is a case for more study with CBD oil only. There is no meaningful research for the use of CBD in ankylosing spondylitis.

History

This case involves a 32-year-old adult male with ankylosing spondylitis. He has daily low back, thoracic and cervical pain and intermittent hip and knee pain. Morning stiffness.

Medication consists of Simponi injection once monthly, and ibuprofen PRN.

He has been married for 5 years, with two young sons. He is a primary school deputy headmaster with an active social life based around his family and local church.

It is postulated that increasing cannabinoids in this subject's system may help in reducing ankylosing spondylitis-related pain.

Pre-trial

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

Self-reported moderate pain levels.

Table 1 Pre-trial scores

PPI	3.00
NWC	20.00
PRI	44.71
PR1 S	31.06
PR1 A	5.22
PR1 E	6.06
PR1 M	2.37
Anxiety Screening	n/a
Change in Pain Levels	

Subject reported pain in jis thoracic and lumbar spine, and pelvic region.

Pain Perception Index (PPI) at 3, 'discomforting'. on the McGill Pain Questionnaire.
This is the patient's perception of their pain level, with a choice of six options, ranging from 0 – none to 6 – excruciating (Melzack 1975).

Number word count (NWC) 20 on the McGill Pain Questionnaire.
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 score 44.71 on the McGill Pain Questionnaire.
This is the total score for all categories, from a possible maximum total of 214 with each word being multiplied by a different ranking applicable to each section. An example 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. Higher numbers indicate more severe levels of perceived pain (Melzack 1975).

Trial

The subject was supplied with a bottle of 10% (1000 ml) Cherry CBD oil, with instructions to take it daily and a jar of EVR Premium Hemp Oil CBD Salve to use topically at pain sites.

No reporting during trial from this subject.

Post-Trial

Pain Perception Index (PPI) at 2, 'mild', on the McGill Pain Questionnaire, a drop from the previous 3, discomforting. 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) 12, lower than the previous 20 . 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 22.15 on the McGill Pain Questionnaire, a significant decrease of 50.46% from the previous overall score of 162.35. This is the total score for all categories, from a possible maximum total of 214 with each word being multiplied by a different ranking applicable to each section. An example 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. Higher numbers indicate more severe levels of perceived pain.

Subject reported that he didn't feel that the CBD product used had been helpful, either topically applied or orally administered. His wife had applied the salve to the whole of his back on several occasions without a noticeable decrease in his pain levels. (His wife however reported using it for her own persistent thumb and low back pain with excellent results, although she wasn't part of this trial.)

The subject attributes his improved pain scores to a new programme of gym exercises for four days every week beginning 3 weeks into the trial. He reported that gym days were good days and continue to be so after the end of the trial. Based on his experience, he would not buy the products as supplied for the trial in future.

Table 2 Post-trial scores

NWC	20.00	12.00

PRI	44.71	22.15
PR1 S	31.06	17.43
PR1 A	5.22	1.74
PR1 E	6.06	1.01
PR1 M	2.37	1.97
Anxiety Screening	n/a	n/a
Change in Pain Levels		50.46%

Discussion

This subject had a significant reduction in pain but it he attributed this to his new exercise regime. This is entirely possible, as exercise is known to improve the function and pain levels in patients with ankylosing spondylitis. There is a possibility that the combination with CBD enhanced this effect, but it cannot be proven by this study.

The effects of oral CBD products in this trial can be neither proved or disproved.

No beneficial affects were shown for the topical CBD products, and in any case, the study protocol was flawed in respect of the CBD topical product. There is no way to separate its potential effects from those of the oral product, and any results that may have been suggested can only be taken as anecdotal. Further double-blinded, controlled trials with large participant numbers are suggested to judge the efficacy of the topical product in isolation from the oral product.

Further study on the effects of oral CBD products in ankylosing spondylitis are suggested, at a higher dose, and with no other changing parameters in eg lifestyle to obfuscate the results.

Author Notes

Jane Sutton BSc (Hons) MCSP Grad Dip Phys MAACP qualified as a physiotherapist in 1983. She has private physiotherapy 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.

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Case Study Report 5

Cannabidiol Oil Trial in Adult Female with Anxiety Disorder and Fibromyalgia

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).

Anxiety disorder is classed as a serious mental illness, with many variants, which include social anxiety, panic and generalised anxiety disorders, plus phobias, Anxiety of itself is a normal reaction to stressors such as exams and tests, life problems and making important decisions, but an anxiety disorder differs in that it can cause such problems that a sufferer is unable to live normally (Journal of Psychiatry online).

The 2014 Adult Psychiatric Morbidity Survey reports that depression and anxiety affect one adult in six in the UK population. Levels in men remain similar to the previous study in 2000, but are rising in women (McManus et al., 2014). Global figures show an incidence of around 10% for anxiety alone (Baxter et al., 2013).

The cause of depression and anxiety is a chemical reaction in the brain leading to abnormal variations in a person's mood (Chen J, 2016). There are high levels of depression and anxiety in those with multiple chronic conditions (MCC) (Banhato et al., 2016).

Research shows that cannabinoid receptors are present throughout the limbic system, and they regulate transmission at neural synapses. Increasing signalling at these receptors decreases anxiety and blocking or removing the related gene produces depressive symptoms (Patel and Hillard, 2009; Hill and Gorzalka 2009).

Repeated stressing of rodents in tests reduces the density of CB1 receptors in the hippocampus (Hill and Gorzalka, 2005), and repeating exposure to the same stressor reproduces anhedonia and depressive behaviours (Rademacher et al., 2008).

There is growing evidence that behavioural and endocrine responses to stress become habituated by the actions of the endocannabinoid system (Patel and Hillard 2008). Healthy endocannabinoid signalling acts as a buffering system in emotional response to stressful events and may lead to more appropriate reactions to stress (Ruehle et al., 2012).

Blessing et al., 2015, suggest that CBD has anxiolytic properties in evidence from human studies, However, this is limited to research in acute cases of anxiety, and a small number of studies. They state that CBD needs to be studied further in chronic cases and could be the way forward for treatment of many anxiety disorders.

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, 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 CB_1 (Howlett et al 1988)and CB_2 (Munro et al 1993) are distributed widely throughout the body, but the CB_1 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 CB_1 nociceptors are more important in pain perception than central ones (Agarwal et al 2007) and stimulation of CB_1 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 20 06).

Fibromyalgia is a condition which causes widespread muscloskeletal pain, fatigue, painful trigger points, and memory, bowel, sleep and mood disturbance.

It is present in about 2% of the population worldwide (Walitt et al., 2016).

Its aetiology is unknown (Mease 2005), but it is associated with disruption in biochemical, metabolic, and immunoregulation systems (Jahan et al., 2012).

It is more common in those with previous medical illness, stress and various pain conditions, combined with reduction in the level of biogenic amines and increased excitatory

neurotransmitters. There is also alteration in regulation of the hypothalamic/pituitary/adrenal axis (Mease 2005).

There is a theory that these changes could be caused by sensitisation of the central nervous system. No single treatment has been completely effective for the condition (Mease 2005).

Walitt et al. (2012) did a review of current research in cannabinoids for fibromyalgia but found that they were all of low quality design, that only nabilone (a synthetic cannabinoid) had been trialled, that results were inconclusive, and that fibromyalgia patients had a low toleration of nabilone. Fitzcharles et al 2016 found that nothing had changed from the findings of Walitt et al in the intervening four years.

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 gastro-intestinal 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).

Research for CBD in anxiety has mostly been done in animals and research with CBD in pain, as cited above, have been done mostly with THC containing compounds. The research to date with cannabinoids and fibromyalgia has been scarce and inconclusive. There is a case for more study with CBD oil only. It was felt that case study research in CBD for anxiety and fibromyalgia pain would add to the existing research base, whilst potentially helping this subject to get their symptoms under control.

History

This case involves a 49-year old adult female who has anxiety, and pain associated with fibromyalgia and other conditions. She also has insulin dependent diabetes mellitus, asthma and osteoporosis affecting her pelvis and both hip joints.

Medication consists of Adcal-D3 750mg x2 x2 daily, BD Viva hypodermic insulin needles, Bendroflumethiazide 2.5mg x 1 daily, clotrimazole pessaries, co-codamol 30mg/500 mg tablets for use PRN, Dapagliflozin 10mg x 1 daily, Humalog KwikPen 3ml 20-30m Lansaprazole 30mg gastro-resistant x 2 daily, Nortryptyline 10mg x 3 daily, Ramipril 5mg x 3 daily, Salbutamol inhaler, Sertraline 50mg x 3 daily, Sirdupla inhaler, Tresiba FlexTouch for injection nightly, Dulaglutide injection x I weekly. She is also taking HRT, but was unable to provide the name

She has been married for 20 years. She worked as a learning support assistant until 4 years ago, when her symptoms became too difficult to manage.

It is postulated that increasing cannabinoids in this subject's system may help in controlling anxiety symptoms and reducing fibromyalgia a and other pain.

Tests And Measurements

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

Psych Central Anxiety Screening Test (Grohol 2018).

Table 1 Pre-trial scores

	Pre
PPI	5.00
NWC	56.00
PRI	162.35
Anxiety Screening	41.00
Change in Pain Levels	

Subject reported pain in multiple areas: severe pain in both hips, longstanding bilateral breast pain and 'lumpiness' (20 years+), irritable bowel syndrome, nausea/stomach churning, fatigue and difficulty concentrating.

Self-reported anxiety was high.

Psych Central Anxiety Screening Test (Grohol 2018) score was 47, indicative of a severe anxiety disorder, supporting her self-reported feelings of anxiety.

Pre-trial, she reported severe pain levels, supported by the scoring pattern on the McGill Pain Questionnaire (Melzack 1975).

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

Number word count (NWC) 56 on the McGill Pain Questionnaire.
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 score 162.35 on the McGill Pain Questionnaire.
This is the total score for all categories, from a possible maximum total of 214 with each word being multiplied by a different ranking applicable to each section. An example 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. Higher numbers indicate more severe levels of perceived pain (Melzack 1975).

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. She was also supplied with a jar of EVR Hemp Oil Salve 50mg CBD to apply topically.

Subjective reporting was that during the trial, she didn't feel that there had been a huge difference.

Results

Psych Central Anxiety Screening Test (Grohol 2018) score was 22, asymptomatic for an anxiety disorder, significantly decreased from the previous symptomatic score of 56

Pain Perception Index (PPI) at 3, discomforting, on the McGill Pain Questionnaire, a drop from the previous 5, horrible. This is the patient's perception of their pain level, with a choice of six options, ranging from 0 – none to 6 – excruciating (Melzack 1975)

Number word count (NWC) 31, considerably lower than the previous 56. 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 score 75.15 on the McGill Pain Questionnaire, a decrease of 53.71% from the previous overall score of 162.35. This is the total score for all categories, from a possible maximum total of 214 with each word being multiplied by a different ranking applicable to each section. An example 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. Higher numbers indicate more severe levels of perceived pain (Melzack 1975).

Subject reported that by the end of the trial, her breast pain and 'lumpiness' had completely gone, her irritable bowel syndrome and nausea/stomach churning had gone, and her stress levels seemed a little better. Her hip pain had not altered and had not been helped by topical application of the CBD salve.

Table 2 Post-trial scores

	Pre	Post
PPI	5.00	3.00
NWC	56.00	31.00
PRI	162.35	75.15
Anxiety Screening	41.00	22.00
Change in Pain Levels		53.71%

Discussion

In this subject, it is highly likely that the CBD product which she used was the cause of her decreased pain symptoms.

It is always impossible to rule out the placebo effect in a trial which isn't controlled and blinded, but the reduction in scores above 30% would seem to rule out only placebo as the cause.

The topical product was ineffective for her localised hip pain (she has osteoporosis affecting both hips in addition to her fibromyalgia).

The study protocol was flawed in respect of the CBD topical product. There is no way to separate its potential effects from those of the oral product, and any results that may have been suggested can only be taken as anecdotal. Further double-blinded, controlled trials with large participant numbers are suggested to judge the efficacy of the topical product in isolation from the oral product.

Anxiety levels had dropped very significantly over the period of the trial, from strongly symptomatic for an anxiety disorder to asymptomatic, and this author is of the opinion that this is due to use of the CBD products. Further robust controlled and double blinded trials are suggested in this area.

In conclusion, CBD at this dosage was effective in significantly reducing this subject's fibromyalgia and anxiety symptoms.

Author Notes

Jane Sutton BSc (Hons) MCSP Grad Dip Phys MAACP qualified as a physiotherapist in 1983. She has private physiotherapy 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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Case Study Report 6

Cannabidiol Oil Trial in Adult Female with Anxiety Disorder and Endometriosis 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).

Anxiety disorder is classed as a serious mental illness, with many variants, which include social anxiety, panic and generalised anxiety disorders, plus phobias, Anxiety of itself is a normal reaction to stressors such as exams and tests, life problems and making important decisions, but an anxiety disorder differs in that it can cause such problems that a sufferer is unable to live normally (Journal of Psychiatry online).

The 2014 Adult Psychiatric Morbidity Survey reports that depression and anxiety affect one adult in six in the UK population. Levels in men remain similar to the previous study in 2000, but are rising in women (McManus et al., 2014). Global figures show an incidence of around 10% for anxiety alone (Baxter et al., 2013).

The cause of depression and anxiety is a chemical reaction in the brain leading to abnormal variations in a person’s mood (Chen J, 2016). There are high levels of depression and anxiety in those with multiple chronic conditions (MCC) (Banhato et al., 2016).

Research shows that cannabinoid receptors are present throughout the limbic system, and they regulate transmission at neural synapses. Increasing signalling at these receptors decreases anxiety and blocking or removing the related gene produces depressive symptoms (Patel and Hillard, 2009; Hill and Gorzalka 2009).

Repeated stressing of rodents in tests reduces the density of CB1 receptors in the hippocampus (Hill and Gorzalka, 2005), and repeating exposure to the same stressor reproduces anhedonia and depressive behaviours (Rademacher et al., 2008).

There is growing evidence that behavioural and endocrine responses to stress become habituated by the actions of the endocannabinoid system (Patel and Hillard 2008). Healthy endocannabinoid signalling acts as a buffering system in emotional response to stressful events and may lead to more appropriate reactions to stress (Ruehle et al., 2012).

Blessing et al., 2015, suggest that CBD has anxiolytic properties in evidence from human studies, However, this is limited to research in acute cases of anxiety, and a small number of studies. They state that CBD needs to be studied further in chronic cases and could be the way forward for treatment of many anxiety disorders.

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 CB_1 (Howlett et al 1988)and CB_2 (Munro et al 1993) are distributed widely throughout the body, but the CB_1 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 CB_1 nociceptors are more important in pain perception than central ones (Agarwal et al 2007) and stimulation of CB_1 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).

Endometriosis is a condition mainly affecting women and girls of child-bearing age, typified by pelvic pain, which is usually worse during menstruation, with severe period pain (bad enough to stop normal activities), pain on micturition/defecation, decreased fertility and pain during or after love-making (NHS Endometriosis 2015).

Causatives are not known, although theories range through genetics, immuno-pathology, retrograde menstruation and migration of endometrial cells (NHS Endometriosis 2015; Burney RO et al., 2012).

Lee et al. (2006) report antiestrogenic effects from cannabis smoke condensate, but not CBD. Sanchez et al. (2012) state that although mechanisms of endometriosis are poorly understood, endometrial cell migration and proliferation seems to be partially modulated by the endocannabinoid system.

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 gastro-intestinal 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).

Research for CBD in anxiety has mostly been done in animals and research with CBD in pain and endometriosis, as cited above, has been done mostly with THC containing compounds, so there is a case for more study with CBD oil only. It was felt that case study research in CBD for anxiety and endometriosis pain would add to the existing research base, whilst potentially helping subjects to get symptomatic relief.

History

This case involves a 27-year old adult female who has had anxiety for ‘as long as she can remember’ and endometriosis with ongoing pain and heavy periods, which was diagnosed in 2017, although symptoms have been present for much longer.

The endometriosis had previously caused her to have regular time off work, but in early 2017 she began a course of cranio-sacral therapy, which has reduced her symptoms considerably. She had no time off work from January/February 2018 until May 2018, when she lost her job. The cranio-sacral therapy is on-going.

Medication consists of fluoxetine 30mg x 1 daily. She had been able to cease her pain medication (previously codeine and co-codamol x 2 x 4 daily) before the start of the trial as a direct result of the cranio-sacral therapy.

She has been married for 3.5 years. She lost her job as a cleaner just before the start of the trial in May 2018. She is a volunteer with the Brownie-Guide movement.

It is postulated that increasing cannabinoids in this subject's system may help in controlling anxiety symptoms and reducing residual endometriosis pain.

Tests And Measurements

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

Self-reported moderate to severe abdominal pain levels.

Psych Central Anxiety Screening Test (Grohol 2018) was administered to establish pre-trial anxiety levels.

Table 1 Pre-trial scores

	Pre
PPI	3.00
NWC	34.00
PRI	75.82
Anxiety Screening	27.00
Change in Pain Levels	

Pain Perception Index (PPI) at 4, distressing, on the McGill Pain Questionnaire.
This is the patient's perception of their pain level, with a choice of six options, ranging from 0 – none to 6 – excruciating (Melzack 1975).

Number word count (NWC) 34.
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 score 75.82 on the McGill Pain Questionnaire. This is the total score for all categories, from a possible maximum total of 214 with each word being multiplied by a different ranking applicable to each section. An example 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. Higher numbers indicate more severe levels of perceived pain (Melzack 1975).

Psych Central Anxiety Screening Test (Grohol 2018) score was 27, indicative of a moderate anxiety disorder.

Treatment

The subject was supplied with a bottle of 1000 Cannabidiol natural flavoured Premium Hemp Oil CBD Tincture and instructed to use it once daily for 6-8 weeks.

Subjective reporting was that during the trial, there was a continuing decrease in pain, but that the subject was unsure if this was due to her cranio-sacral treatment or the CBD oil.

Results

Pain Perception Index (PPI) at 3, 'discomforting', on the McGill Pain Questionnaire, an improvement from the previous 4, 'distressing'. This is the patient's perception of their pain level, with a choice of six options, ranging from 0 – none to 6 – excruciating (Melzack 1975).

Number word count (NWC) 23, a reduction from 34.
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 score 49.47 on the McGill Pain Questionnaire, a non-significant decrease of 34.75% from the previous overall score of 75.82.This is the total score for all categories, from a possible maximum total of 214 with each word being multiplied by a different ranking applicable to each section. An example 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. Higher numbers indicate more severe levels of perceived pain (Melzack 1975).

Psych Central Anxiety Screening Test (Grohol 2018) score was down to 16, which is asymptomatic for an anxiety disorder.

Subject reported that her anxiety and pain had both improved, but she was unable to tell if this was due to the cranio-sacral treatment that she had been having, or due to use of the CBD oil. Her pain levels had been steadily dropping prior to the trial as a result of the cranio-sacral therapy treatment, which is on-going on a weekly basis. She has been able to start a new job, which she loves. This commenced some weeks after the end of the trial.

Table 2 Post-trial scores

	Pre	Post
PPI	3.00	2.00
NWC	34.00	23.00
PRI	75.82	49.47

Anxiety Screening	27.00	16.00
Change in Pain Levels		34.75%

Discussion

In this subject, it is impossible to establish whether the helpful factor in further decreasing her endometriosis pain was the concurrent treatment that she was having with cranio-sacral therapy, or usage of the CBD product.

Her anxiety levels had dropped very significantly over the period of the trial, and this author is of the opinion that this could be either to do with a continuing reduction in her pain, or the use of CBD products. It is therefore suggested that the Anxiety questionnaire be re-administered in 8 weeks to see if anxiety levels have increased again after stopping the CBD oil. However, as her activities of daily living have improved, and she has a new and enjoyable job, it may be difficult to establish.

The conclusion that this author has to draw is that the CBD products supplied to this subject have an inconclusive effect in her test result improvements.

Author Notes

Jane Sutton BSc (Hons) MCSP Grad Dip Phys MAACP qualified as a physiotherapist in 1983. She has private physiotherapy 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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