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

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

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

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