

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

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

CBD also promotes signalling of the A_{2A} 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 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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