Submission No 64

INQUIRY INTO USE OF CANNABIS FOR MEDICAL PURPOSES

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Submission to the NSW Parliament

USE OF CANNABIS FOR MEDICAL PURPOSES (INQUIRY)

My name is **Mark Heinrich**. I live in Canberra and I am 57 years old. I use medical cannabis to treat my illnesses. I am a researcher with Cannabis Science Australia, an exciting new Australian business that is looking to develop cannabis-based medicines in Australia to treat skin cancer at an affordable for all Australians.

I am a Veteran of the War on Drugs, and I am a survivor.

What I bring to the Committee with my submission is 35 years of cannabis cultivation/breeding experience, with a deep understanding of the clinical application of medicinal cannabis. I am a medical cannabis educator and patient advocate, and was recently appointed as an advisor to the Thai Government, through the Thai Cannabis Corporation. This position is as cultivation advisor and specialist on the application of cannabis in the treatment of human illness. I have experience in preparation and use of tinctures of cannabis to treat chronic and debilitating Post Traumatic Stress Disorder (PTSD), and chronic neuropathic pain (Allodynia).

My experience with medicinal cannabis highlights that it has provided better outcomes than any single or combination, conventional medicine to treat my disabilities (chronic neuropathic pain, PTSD, depression, and Allodynia).
I am an advocate for the use of medicinal cannabis for Australian's having met with government and law enforcement bodies in an attempt to bring about awareness and ultimately law reform for the use of medicinal cannabis in Australia. I am also a published author in several international medical cannabis magazines.

This is my story and my submission to the **Use of cannabis for medical purposes (Inquiry). I am also including a statement from my colleague, Nevil Schoenmakers**, who is without doubt the world's foremost breeder of medical cannabis genetics. I am also including a statement from Professor Manuel Guzman in Spain, when I address my recent cancer scare and my choice to use a cannabis extract as a primary treatment to kill off the cancer.

Before I fell ill I was a regular every day Aussie guy. I was working in the Federal Department of Veterans Affairs as a senior officer during the Agent Orange years and the setting up of the Vietnam Veterans Counselling Service. It was exciting times and I was achieving in life. I had the two kids, a mortgage, a beautiful wife, and a dog of course. Also, I was very fortunate to have played sport at the international level, and was fortunate enough to have been selected as captain of the Australian National Broomball Team on two tours of Canada (in 1988 and again in 1991), including the inaugural World Championships held in Victoria, British Columbia, Canada. (See image attached of me with the 1991 National Team in Canada – I am #6 in the image).

They were my halcyon days.

However....

I am also a sufferer of the insidious illness known as Post Traumatic Stress Disorder. It has plagued my life for nearly 35 years. It has cost me a wife, my home, my kids, and finally, my sanity. It took me to the depths of despair, and led me into a life of poly-drug use in an attempt to escape the horrors of my mind. There seemed no escape.

You see, I am a survivor of being locked up in 1977 in Sagmalicar Prison in Istanbul, Turkey. A youthful adventure, not involving drugs, that went terribly wrong. I had been caught smuggling cars from Munich to Tehran and paid a dreadful price.

It was not until I started to hear reports that cannabis was a valuable tool in dealing with PTSD that I began to feel some hope that things may change for the better.

In order to alleviate my symptoms and pursue a normal life style I turned to a tincture of cannabis with successful results.

The relaxing, and anxiolytic (anti-anxiety) effects of cannabis under some conditions has been known for centuries but it is only recently that I have begun to understand the complex way in which cannabinoids and the endocannabinoid (eCB) system modulate the expression of anxiety-type behaviour. I found immediate relief, but in a way that I least expected, and in a way that few others had discussed. I found that Cannabis suppressed my dreams!

There is a lot of science about how cannabis disrupts REM, in particular Delta 4 and Delta 5 stages of sleep. This sleep disruption was seen as a deleterious side effect of cannabis use. My observations were that quite the opposite was the case. I found it a necessary and beneficial side effect! The tincture of cannabis immediately became the primary treatment for my PTSD.

For sufferers of PTSD, nights can be a difficult time. The persistent night terrors and nightmares can destroy the quality of life. They become a constant reminder of the past, and from a clinician's point of view, are very difficult to treat.

This is my story and my journey to recovery. It is not written as a scientific treatise. I share this with you to highlight another wonderful aspect of medicinal cannabis, and hope others will learn and benefit from my personal account.

The Dreaming

Some 15 years after my release from Sagmalicar Prison in Istanbul, Turkey, I began having night terrors and nightmares on a regular occurrence. I would wake several times during the night, filled with fear and drenched with sweat. It would always be the same dreams, night after night after night. My life slowly started to unravel, and my world began to be filled with anxiety and fear. I dreaded going to bed because as

soon as I turned the lights off, my mind fell back into the deep dark horrors of Sagmalicar.

I soon became dysfunctional and my marriage collapsed. I fell into a sad life of poly-drug use, and began to sense a strong feeling of social exclusion. I felt incredibly alone. I was quite literally dying, both physically and emotionally.

The dreams came and went with an increasing frequency and intensity. I tried everything from strong sedatives to prolonged sessions of cognitive therapy with a Forensic psychologist. It was one step forward and two steps back. There was just no escaping the simple fact that I eventually needed to sleep, and that was when all the therapies in the world could not help. When the lights went out and I fell into the dark, my mind took me further into the dark. I was desperate to find answers.

I began to look for answers.

Reclaiming the Night

One advantage of growing older is that you can look back on the past and see patterns in your life. I had noticed over the years that when I smoked cannabis, my PTSD symptoms seemed lessened. I found in particular that my anxiety levels were diminished, and that depending on the strain of cannabis I was smoking, my moods were also modulated to tolerable levels. This was a critical observation as depression had set in as a result of my anxieties and sleep disorder. I noticed also that I was able to sleep through the night without dreaming. It was the absence of dreams that truly was the key to finding the answers that no doctors or psychologists could give to me.

I started looking on the internet and could find nothing on cannabis and dream suppression. Sure, there was plenty of info on PTSD and the wonderful results from using cannabis as a primary treatment regimen, but nothing specifically on REM and dream suppression.

I then made a decision that I would need to be the master of my own destiny, so I devised a cannabis-based treatment regimen, specifically tailored to meet my needs. I began to source cannabis strains that I knew to be efficacious in mood modulation and dream suppression. I collected genetics from around the world and began studying the results of my observations.

The Science of Cannabis and PTSD

* I apologise for the long read but this is perhaps the best summary of scientific references on cannabis to treat PTSD*

Post Traumatic Stress Disorder (**PTSD**) results from extreme attack on psychological wellbeing involving threat of loss of life or intense physical harm. Individuals stricken with this malady frequently find themselves reliving the memories of the trauma through “flashbacks” during waking hours and night terrors and nightmares when

asleep, the latter two resulting in insomnia which further compromises psychological wellbeing. PTSD can completely undermine an individual's attempts to operate as a functional member of society.

Who develops PTSD, you might ask? Historically, veterans have brought the most attention to this condition as is made evident by the older names "Shell Shock" and "battle/combat fatigue". This is despite the fact that soldiers only compose one group suffering from this condition. As of yet, there are no known cut and dry rules about exactly who will or who won't develop PTSD. Depending on the severity, in 5%-80% of individuals, experiencing one of the following events will trigger onset of the disorder: violent military duty, car accidents, domestic abuse, surgery, sexual abuse/assault, child abuse, torture, terror tactics, severe natural disasters, etc (Wikipedia, 1). The following quote typifies the life of many PTSD suffers:

"I've been a deputy sheriff as well as a police chief and a private investigator, but the PTSD always made me crash and burn. I've lost everything several times, and for the last few years I have been rebuilding again. My doctors have told me to retire and try to maintain as normal a life as possible."

- Michael McKenna, http://www.rxmarihuana.com/pstd.htm

In order to alleviate their symptoms and pursue a normal life style many suffers turn to cannabis with successful results. The relaxing, and anxiolitic (anti-anxiety) effects of cannabis under some conditions have been know for centuries but it is only recently that we have begun understand the complex way in which cannabinoids and the endocannabinoid (**eCB**) system modulate the expression of anxiety-type behavior.

There are three main factors that are important to the study and understanding of PTSD. These are aversive memory formation, if the aversive memory or fear is cue-induced vs contextual, and finally the extinction of the aversive memory or fear. In humans, aversive memory formation occurs during the traumatic event(s) that initiate PTSD. In animal models of PTSD, a mild but inescapable foot shock or repeated loud tones can form aversive memories in rodents. In humans, a vet easily startled by loud noises would be experiencing cue-induced fear where as an accident victim having a panic attack from the feeling of being in the driver's seat of a car has experienced contextual fear. For rodents in the lab, cue-induce fear is produced by the repeated pairing of a loud noise with a foot shock a second later. The cue-induce fear is expressed by the rodent when it is next exposed to the noise. Contextual fear in the lab is often elicited by the pairing of a series of loud tones with a unique environment. The contextual fear is expressed when the rodent is later placed in the same unique environment minus the tones. Extinction of the aversive memory for both lab animals and humans usually involves repeated exposure and habituation to the cue or context that elicits the fear minus the original fearful stimulus until fear is no longer elicited by that cue or context. For the accident victim this would be getting in the car, then the drivers seat and then actually driving. For the mouse who was shocked after hearing a loud noise it would be repeatedly hearing that noise

without experiencing foot shock. There are other factors of PTSD in humans which are important to treatment but are not necessary for the study of PTSD in the lab.

Recent advancements in the understanding of the eCB system and how it helps modulate the formation of memory and responses to stress have provided researchers with an explanation of how cannabis can act as a successful treatment agent for PTSD. Fride, et al., 2005 found that mice lacking the cannabiniod-1 (**CB1**) receptor, the receptor responsible for the effect cannabis has on the central nervous system (**CNS**), were significantly more likely to experience behavioral inhibition after repeat cue-induced stress as compared to wild type mice not lacking the CB1 receptor. Behavioral inhibition is one animal model of PTSD. These findings gave support to the theory that the cannabinoid system could effect the formation of PTSD. Further evidence comes from the location of CB1 receptors in the brain. The brain regions responsible for controlling memory formation and emotion also contain large numbers of CB1 receptors, (Joy, et al., 1999). In 2003, Costanzi, et al., also found that anandamide, the endogenous ligand for the CB1 receptor, dose-dependently inhibited stressful memory formation. Chronic stress has been found to produce cognitive impairment which is attenuated by the administration of cannabinoids. The same chronic stress was also found to produce significant downregulation (reduction in density) of CB1 receptors and decreases in amount of anandamide found in the hippocampus. The hippocampus is involved with the formation of complex contextual memories. These findings led the researchers to suggest deficiencies in CB1 receptor densities and/or production of anandamide in the hippocampus were critically involved in the development of the behavioral inflexibility and a tendency to perseverate and ruminate that are part of the symptomological profile of such stress induced neurological disorders as PTSD, (Hill, et al., 2005).

In 2002, Marsicano, et al. concluded that the endocannabinoid system was also involved with the extinction of cue-induced adverse memories. They determined this action was achieved through inhibition of **GABA** (gamma-aminobutyric acid) by way of pre-synaptic modulation of GABA release in the amygdala via activation of CB1 receptors. They also found anandamide levels were elevated in the basolateral amygdala (**BLA**) during memory extinction tests. The BLA is a brain region known to be involved with extinction of cue-induced fear (Tomaz, Dickinson-Anson, & McGaugh, 1992). It was later confirmed that synaptic transmission of GABA was decreased in the BLA by activation of the CB1 receptor (Azad, et al., 2003).

Since Marsicano's study in 2002, the dependence of extinction of cue-induced fear responses on the eCB system has begun to gained general acceptance by the scientific community (Chhatwal, et al., 2005; Mikics, et al., 2006; Kamprath, et al., 2006; Pamplona, et al., 2006; Niyuhire, et al., 2007; Varvel, et al., 2007). At the same time a more complex and complete picture has started to appear. One emerging trend points to modulation of the eCB system as more effective at aiding in extinction than direct activation of the CB1 receptor via an exogenous cannabinoid like THC (Chhatwal, et al., 2005; Patel & Hillard, 2006; Varvel, et al., 2007). At best, facilitation of extinction by exogenous cannabinoids is dependent on species and

breed of rodent and on the cannabinoid tested, in the studies that have been carried out so far (Pamplona, et al., 2006). In most cases though exogenous cannabinoids like THC and WIN55212-2 produce no detectable change in extinction rates of cue-induced fear at doses tested. Modulation of the eCB system via inhibition of fatty-acid amide hydrolase (**FAAH**) appears to be a very promising means of facilitating extinction of cue-induced fears. FAAH is the primary enzyme responsible for the metabolic breakdown of anandamide. Inhibiting FAAH increases intercellular levels of anandamide and thus enhances the ability of anandamide to activate the CB1 receptor. In this way inhibition of FAAH appears to reliably facilitate extinction (Chhatwal, et al., 2005; Patel & Hillard, 2006; Varvel, et al., 2007). One recent study even found that mice with either genetically or pharmacologically compromised FAAH not only exhibited faster extinction rates in a spatial memory task but also faster rates of acquisition/learning of the task in the first place (Varvel, et al., 2007). Chhatwal and colleagues, 2005, also found that upon subsequent foot-shock rats treated with a FAAH inhibitor were less likely to re-acquire fearful behaviors after extinction than were none-treated animals.

The situation is not so clear for contextual fears. With contextual fear it is the context/environment that induces the fear response. This is in contrast to cue-induced fear where the presentation of a stimulus such as a loud noise elicits the fear response. Two different brain structures are responsible for cue-induced and contextual fear, the amygdala and the hippocampus, respectively. Therefore it might be expected that cannabinoids would effect these two types of fear differently. Early findings suggest this is the case. In 2006, Mikics and colleagues exposed rats to short sessions of foot-shocks and 24 hours later tested their fear response to the environment in which the shocks had occurred. They found that when WIN55212-2 was administered prier to behavioral testing 24 hours after the rats received shock an increase in the expression of contextual fear was observed. A CB1 receptor antagonist blocked this effect and when administered alone reduced the intensity of contextual expressed by the rats. In other words cannabinoids made them more afraid, while blocking cannabinoids reduced fear. One implication of this finding is that exogenous cannabinoids like smoking cannabis could exacerbate the experience of preexisting contextual fears.

If only things were that simple. Later the same year, Pamplona and colleagues found that WIN55212-2 facilitated extinction of contextual fear in rats both immediately and 30 days after acquisition of contextual fear. Furthermore, the CB1 receptor antagonist rimonabant disrupted extinction both immediately and at the 30 day fear extinction sessions. It is clear the role of cannabinoids in contextual fear requires further elucidation before we can predict how cannabinoids will effect this more complex form of associative fear learning.

People suffering from PTSD often also experience affective disorders like major depression or bipolar disorder and generalized anxiety disorder. They also experience increased startle response, irritability, nightmares/terrors, and insomnia. One theory proposed by Hill and Gorzalka in 2005 suggested that the eCB system

plays a major role in major depression. First they site the fact that both the genetic disruption and pharmacological blockade of the CB1 receptor resulted in a state analogous to major depression and generalized anxiety, two closely related disorders. Hill and Gorzalka also point out that the eCB system is down-regulated by chronic stress. There is also evidence that the eCB system is involved with the regulation of stress and general anxiety. In general, genetic CB1 receptor deficits or pharmacological blockade of CB1 receptors both produce anxiety and depression in rodents. Where as FAAH inhibition produces anxiolitic effects (Viveros, Marco, & File, 2005; Carrier, Patel, & Hillard, 2005). In a test of general anxiety in mice Patel and Hillard, 2006, found that the CB1 agonists WIN5212-2 and CP 55,940 (40 times more potent than THC) both produced an anxiolitic effect at the lowest dose tested. THC however was found to produce a dose-dependent anxiety-like response. One FAAH/anandamide-uptake inhibitor produced an anxiolitic effect at lower doses but had no effect at the highest dose tested while another pure FAAH inhibitor produced only a dose-dependent anxiolitic effect.

It has long been thought that the neurotransmitter serotonin plays a role in depression and anxiety. Braida et al., 2007 found that both THC and an anandamide uptake inhibitor were dose-dependently anxiolitic and that this was blocked by a serotonin 1A (5-HTA1) receptor antagonist. They also found that co-administration of a sub-threshold dose of a 5-HTA1 receptor agonist with a sub-threshold dose of either THC or the uptake inhibitor produced a synergistic anxiolitic effect together. This led them to conclude that serotonin played a modulatory role in the anxiolitic effect of both exogenous and endogenous cannabinoids.

Estrogen produces anxiolitic and anti-depressant effects. Estrogen has been shown to regulate FAAH. Hill, Karacabeyli and Gorzalka, 2007, found that estrogen induced anxiolitic properties were blocked but the administration of a CB1 receptor antagonist. Furthermore, FAAH inhibition produced much of the same anxiolitic effects as estrogen in the tasks tested. This led the researchers to conclude that FAAH inhibition might be a viable treatment option for depression and anxiety disorders in women. This is also important to PTSD since the lifetime prevalence of PTSD in women (10.4%) is a little more than twice as high as in men (5%) (Wikipedia, 1). Again, this provides further evidence that eCB modulation should be a pharmacological target of future anxiety treatments.

As stated above, issues with sleep also afflict PTSD suffers. In rats, anandamide changes sleep patterns by increasing slow-wave sleep and REM sleep at the expense of wakefulness (Murillo-Rodríguez, et al., 2001). Sleep deprivation also produces increases in slow-wave sleep and REM sleep once sleep does occur. This phenomenon is known as the rebound effect or sleep rebound. Navarro et al., 2003 found that administration of a cannabinoid antagonist before sleep rebound prevented the REM rebound and that sleep deprivation did not change CB1 receptor densities in rat brains. However sleep deprivation plus 2 hours sleep rebound increased CB1 receptor densities in rat brains. Therefore it appears that changes in the eCB system play a role in the rebound effect. Because THC and anandamide increase sleep in humans and other mammals, Murillo-Rodríguez, et al., 2003,

investigated whether or not adenosine, a sleep-inducing nucleoside, might be involved in cannabinoid induced sleep. During the third hour after administration of anandamide, intracellular adenosine levels peaked in rat basal forebrains. Peak adenosine levels were accompanied by a significant increase in slow-wave sleep during the third hour after anandamide administration. Both the induction of sleep and the rise in adenosine levels were blocked by the administration of a CB1 receptor antagonist. Together, these findings led the researchers to suggest that the eCB system may be a pharmacological target of treatment for conditions that produce severe sleep disruption such as PTSD.

All these indications that the CB1 receptor and anandamide may play a role in stress and memory has led the Israeli military to start an investigation into treating PTSD in their soldiers with therapeutic cannabis. In 2004 at Jerusalem's Hebrew University, Raphael Mechoulam started studying the effects of orally administered delta9-THC, the active ingredient in cannabis, on 15 Israeli soldiers suffering from PTSD acquired during combat in the Gaza Strip. Although the study is still in progress, Mr Mechoulam stated that, as one might expect based the studies discussed above, cannabis “helps them sleep better, for one thing. These people often wake up from nightmares and experience sweating or hallucinations” (Heller, 2004).

Despite the anecdotal evidence to the contrary, most of the experimental studies that have been conducted so far indicate that by and large the administration of exogenous cannabinoids such as vaporizing therapeutic cannabis may not be the most reliable nor effective means of utilizing the eCB system to treat anxiety and aversive memories such as those formed in PTSD. For reliable and truly effective treatment of these conditions it appears that restricting eCB breakdown by way of FAAH inhibition is the best target discovered so far within the eCB system. (The other eCB targets include the two primary receptors CB1/CB2, vanilloid receptors, eCB reuptake, as well as eCB production.) To this end, Kadmus Pharmaceuticals, Inc. has started to express serious interest in marketing a new FAAH inhibitor they have developed, currently code-named KDS-4103. KDS-4103 appears to have a lot of potential from a pharmacological perspective. Even though it produces analgesic, anxiolitic, and anti-depressant effects it otherwise does not produce a classic cannabis-like effect profile and animals easily discriminate between THC and KDS-4103. All this indicates that KDS-4103 does not produce a “high” like THC and other direct CB1 agonists. KDS-4103 is orally active in mammals and fails to elicit a systemic toxicity even at repeated dosages of 1,500mg/kg body mass. All other available evidence to date also suggests a very high therapeutic margin for KDS-4103. All in all, considering that the kinds of events which usually precipitate PTSD in most individuals often also involve pain, KDS-4103 seems like it may be just about the perfect medication.

So what should all this mean to the individual? Anecdotal evidence says by and large the use of therapeutic cannabis provides a significant improvement in quality of life both for those suffering from this malady and for their family and friends. Whether or not this is taking the fullest advantage possible of the eCB system in the treatment of PTSD is yet to be seen. Mostly the use of cannabis and THC to treat PTSD in

humans appears to provide symptomological relief at best. In and of itself, there is nothing wrong with symptomological relief. That's what taking aspirin for a headache, a diuretic for high blood pressure, opiates to control severe pain, or olanzapine for rapid-cycling mania is all about. We do have the potential, however, to do better than just treating symptoms of PTSD via activation of the cannabinoid receptors. With the right combination of extinction/habituation therapy and the judicious administration of a FAAH inhibitor like KDS-4103 we have the potential to actually cure many cases of PTSD. For the time being though, symptomological treatments are all we have for more generalized anxiety and depression disorders.

If an individual were to want to get the most out of using therapeutic cannabis to improve a PTSD condition they should try to use low to moderate doses with as stable a blood level as possible for general anxiety and depression symptoms. Oral cannabis produces more stable blood levels. Since peak levels will produce the most soporific effect, administration of oral cannabis right before bed should produce the most benefits for improving sleep patterns. If the goal is to use cannabis to facilitate extinction of the response to PTSD triggers than small to moderate doses of cannabis vapors should be administered shortly before planned exposure to the trigger. A series of regular extinction sessions will produce better results than a single session. If cannabis appears to make aversion, fear, or aversive memories worse then the dosage should be lowered. If feelings of fear do not improve with lower dose then discontinue use of cannabis as fear-extinction aide.

In light of all evidence currently available, it is striking that the USFDA refuses to investigate cannabinoids for the treatment of anxiety disorders like PTSD yet they have approved studies of MDMA, the club drug Ecstasy, for the treatment of PTSD (Doblin, 2002). Even if you do not accept cannabis as the answer itself, it should be hard to accept that by and large we still have not found effective and reliable ways to utilize the eCB system in modern western medicine. After all, the most potent (meaning it takes the least amount to produce a threshold effect) substance know to humans is not LSD as many still assume but is instead a derivative of fentanyl, know as Carfentanil. The threshold dosages for LSD and Carfentanil are 20-30µg (micrograms) and 1µg, respectively (Wikipedia, 2 & 3). This makes Carfentanil 10,000 times more potent than morphine, 100 times more potent than fentanyl, and 20-30 times more potent than LSD. At least up until 2005 and unlike LSD, Carfentanil was(is?) regulated as a Schedule II substance in the US (Erowid). For those that do not know, this means that despite perceived extreme dangers from use or abuse of this drug it is still assumed to have medical value. With the lives and well being of so many veterans AND private citizens at stake, those in the scientific community and police makers alike cannot afford to miss the wake up call. Even a child should be able to see the hypocrisy evident in the relative policies concerning cannabinoids and opiates. It is time to fix this appalling imbalance in our policies concerning the pharmacopia or else be the laughing stock of future generations.

MITIGATION OF POST-TRAUMATIC STRESS SYMPTOMS BY CANNABIS RESIN: A REVIEW OF THE CLINICAL AND NEUROBIOLOGICAL EVIDENCE.

Abstract

It is known from clinical studies that some patients attempt to cope with the symptoms of post-traumatic stress disorder (PTSD) by using recreational drugs. This review presents a case report of a 19-year-old male patient with a spectrum of severe PTSD symptoms, such as intense flashbacks, panic attacks, and self-mutilation, who discovered that some of his major symptoms were dramatically reduced by smoking cannabis resin. The major part of this review is concerned with the clinical and preclinical neurobiological evidence in order to offer a potential explanation of these effects on symptom reduction in PTSD. This review shows that recent studies provided supporting evidence that PTSD patients may be able to cope with their symptoms by using cannabis products. Cannabis may dampen the strength or emotional impact of traumatic memories through synergistic mechanisms that might make it easier for people with PTSD to rest or sleep and to feel less anxious and less involved with flashback memories. The presence of endocannabinoid signalling systems within stress-sensitive nuclei of the hypothalamus, as well as upstream limbic structures (amygdala), point to the significance of this system for the regulation of neuroendocrine and behavioural responses to stress. Evidence is increasingly accumulating that cannabinoids might play a role in fear extinction and antidepressive effects. It is concluded that further studies are warranted in order to evaluate the therapeutic potential of cannabinoids in PTSD.

The Endocannabinoid System and Extinction Learning

Abstract

The endocannabinoid system has emerged as a versatile neuromodulatory system, implicated in a plethora of physiological and pathophysiological processes. Cannabinoid receptor type 1 (CB1 receptor) and endocannabinoids are widely distributed in the brain. Their roles in learning and memory have been well documented, using rodents in various memory tests. Depending on the test, the endocannabinoid system is required in the acquisition and/or extinction of memory. In particular, the activation of CB1 receptor-mediated signaling is centrally involved in the facilitation of behavioral adaptation after the acquisition of aversive memories. As several human psychiatric disorders, such as phobia, generalized anxiety disorders, and posttraumatic stress disorder (PTSD) appear to involve aberrant memory processing and impaired adaptation to changed environmental conditions, the hope has been fuelled that the endocannabinoid system might be a valuable therapeutic target for the treatment of these disorders. This review summarizes the current data on the role of the endocannabinoid system in the modulation of extinction learning.

The Cannabinoids as a Primary Medical Treatment

Historically, the use of medical marijuana principally was administered by smoking, but over the last 40 years there have been pharmacological advances in the way that cannabinoids are utilised for medicinal purposes (Kennen, 2008, Pertwee, 2006). Cannabinol was the first of the plant cannabinol's to be discovered from a red oil extract of the cannabis plant at the end of the 19th Century. From this discovery, the chemical structure of the plant was revealed in the early 1930's and from that a synthetic chemical structure was developed in the USA in the 1940's. Cannabidiol (CBD) was isolated shortly afterwards (Pertwee, 2006). Following on from these discoveries, THC was first isolated from the cannabis plant in 1942 and together with CBD were synthesised in 1963 (CBD) and 1964 (THC) (Pertwee, 2006).

While pharmacological experiments with the early cannabinoids occurred as early as the 1940's/50's, it was the 1960's and 1970's that saw testing of cannabinoids increase markedly. These experiments and trials were spurred on at the time by a virtual explosion of marijuana/cannabis use amongst young people in particular across the Western world (Pertwee, 2006).

In the mid 1980's it was discovered that cannabinoid receptors exist within the human body and that THC was able to bind to these receptors to either act with them or block them (Pertwee, 2006, Kennen, 2008).
The two receptors are known as CB1 and CB2 receptors. CB1 receptors are located primarily in the brain and CB2 receptors are located primarily in the immune cells, (Kennen, 2008). With the discovery of the cannabinoid receptors within the body, the development of synthetic cannabinoids that influence these receptors took place in the 1980's/1990's (Pertwee, 2006).
Cannabinoids have been used successfully since these discoveries (in those regions where cannabinoid treatment is legalised, similarly to its use in ancient times) to reduce pain and discomfort in people with debilitating diseases and conditions such as cancer (the nausea and vomiting caused by chemotherapy), multiple sclerosis (the muscle spasticity associated with MS and epilepsy) and the neuropathic pain and body wastage associated with HIV/AIDS and cancer (Seamon, et al, 2007).
Currently there are two forms of medicinal cannabinoids used in reducing pain in people living with HIV while also stimulating the appetite. These are smoked marijuana and oral tetrahydrocannabinol (THC, dronobinol and marinol). The difference between each is significant. Oral THC is considered safe, is delivered in standardised doses but has a slow onset (peak effects in around 120 minutes). However, due to this slow onset, users find it difficult to regulate the dose to achieve the required effect. Conversely, smoked marijuana has a relatively rapid onset and its effects can be felt almost immediately (Seamon, et al, 2007), with peak effects felt in users in around 20 minutes (Haney, et al, 2005). The cannabinoid travels from the
lungs to the blood stream and to a number of the body's organs expeditiously (Seamon, et al, 2007) and as such, users can more closely regulate the dose that is necessary to deliver the required effect (Haney, et al, 2005).

I would like now to put forward the input I referred to in my opening, from Mr Nevil Schoenmakers; as part of my submission to the Committee.
Mr Schoenmakers is perhaps the best person in the world to be called on to speak about cannabis in this Parliamentary Committee. Quite apart from being my friend, he is perhaps responsible for 90% of the commercial cannabis strains that are currently available on the global market. His experience and wisdom I hold in the highest regard. This is the first time Mr Schoenmakers has spoken publicly since 1986. It is the nature of the cannabis industry to live quiet lives, and it is a very rare opportunity indeed to have his input.

Submission Comment by Nevil Schoenmakers

Medicinal cannabis covers a wide range of strains of cannabis, each having a different cannabinoid profiles. The issue is further complicated by the fact that different people respond differently to the same cultivar. What makes one person feel good can have the opposite effect on another. The reason that this needs emphasizing is that there is a mistaken belief that isolating individual cannabinoids and administering them singly or adding a couple together in predetermined ratios will cater to the needs of all. The lack of acceptance of the GW Pharmaceuticals product Sativex clearly demonstrates this. Trying to squeeze cannabis in the standard pharmaceutical company mould of isolating or synthesising cannabis components coupled with the attendant patents to guarantee property rights, will ultimately be at best only partially successful. This will still leave the majority of legitimate medical users dependant on the black market or force them to grow their own illegally.

(a) the efficacy and safety of cannabis for medical purposes;

To the best of my knowledge, no one has died from an overdose of cannabis and most people attending the emergency centres at hospitals are merely having anxiety attacks, brought on by ingesting (as opposed to smoking) quantities of cannabis that brings them out of their comfort zone. Smokers are generally more able to regulate the amount of cannabis needed to achieve the desired effect because the effect is more immediate. More guidance is required for patients who need to ingest cannabis for that particular form of treatment, although overdoses are not fatal and have no lasting ill effects, large doses can cause anxiety. Topical applications of cannabis extracts are completely safe and do not have a psychoactive effect.
With regard to treatments where patients are using medicinal cannabis for what I would loosely describe as psychological problems, it's a question of subjective analysis. In other words, if the patient says,"I feel better", then it works. With regard to more objective ailments, i.e. skin cancer, I refer you to the evidence provided by my colleague Mr. Mark Heinrich.

(b) if and how cannabis should be supplied for medical use;

In many or most cases patients are quite capable of providing for their own needs and providing that the production is limited to their own needs, I see no need to interfere with their common law right to do so. The amount of plants required will depend on the type of treatment being used. Juicing cannabis has proven to be particularly effective for a wide range of ailments. See attached YouTube video

By necessity more cannabis will need to be grown for this method and it does not lend itself to production by third parties. It needs to be fresh. Self sufficiency ensures that the costs do not have to be covered by an already over burdened health care system.

Tinctures and extracts which necessitate the use of solvents are best produced by those specialized in such matters and surely falls within the jurisdiction of the Therapeutic Goods Association.

For those unable to produce medicinal cannabis for their own use, I would advocate production by licensed growers who in effect can only grow for a state sponsored governing body, which in turn deals with the distribution of the product. This will have the effect of breaking the link between the grower and that patient, thereby ensuring a transparent system.

(c) legal implications and issues concerning the use of cannabis for medical purposes;

A countries laws, especially those who are members of the United Nations, are governed by the International treaties they have signed.

There are two treaties to which Australia is a signatory that are relevant to the subject at hand.

Firstly ; THE SINGLE CONVENTION ON NARCOTICS DRUGS OF 1961

For the first time, cannabis was added to the list of internationally controlled drugs. In fact, regulations on the cannabis plant – as well as the opium poppy, the coca bush, poppy straw and cannabis leaves – were embedded in the text of the treaty, making it impossible to deregulate them through the normal Scheduling process. A 1962 issue of the Commission on Narcotic Drugs' *Bulletin on Narcotics* proudly announced that "after a definite transitional period, all non-medical use of narcotic drugs, such as opium smoking, opium eating, consumption of cannabis (hashish, marijuana) and chewing of coca leaves, will be outlawed everywhere.

The Single Convention places the same restrictions on cannabis cultivation that it does on opium cultivation. Article 23 and Article 28 require each Party to establish a government agency to control cultivation. Cultivators must deliver their total crop to the agency, which must purchase and take physical possession of them within four months after the end of harvest. The agency then has the exclusive right of "importing, exporting, wholesale trading and maintaining stocks other than those held by manufacturers."

Thus, should Australia wish to allow the medical use of cannabis and comply with the Single Convention, a government agency must be created to control cultivation along similar lines as those regulating medical opium production. Opium production is regulated by the Department of Justice through the "Poppy Advisory and Control Board".

A similar approach has been adopted by the Netherlands in creating **"The Office of Medicinal Cannabis" B.M.C.**

Secondly, Australia is also party to The **United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.**

This treaty amended the 1961 treaty regarding the definition of cannabis to;

ARTICLE 1 DEFINITIONS

(b) "Cannabis plant" means any plant of the genus Cannabis.

The Single Convention of 1961 specifically excluded the seeds of the cannabis plant.
(d) any other related matters.
The **COMMONWEALTH OF AUSTRALIA**
being... A company registered with the Securities Exchange Commission in Washington DC, USA, CIK#: 0000805157,
is party to the two above mentioned international treaties. Being the corporate governing body of Australia, it has jurisdiction relating to matters of commerce, hence my recommendation that in all matters relating to commerce, the letter of the law must be adhered to as stipulated by the treaties.
The Commonwealth of Australia also benefits from being signatories of the above mentioned treaties in the form of licenses granted by the
United Nations International Narcotics Control Board to produce approximately 25% of the worlds medical opium in Tasmania. The Poppy straw is processed by three multinational corporations in Victoria for the pharmaceutical industry. It is conceivable that non compliance of the terms of the treaty may lead to threats of sanctions, such as the withdrawal of this license, although I doubt that it would be in anyone's interest to do so. In any case, the production of high quality medical grade cannabis can be exported to other countries once the regulatory bureau has been created. The economic interests may rival or exceed those of opium production as Australia is well positioned geographically to produce a high quality medicinal product.
I don't know how much economic benefit Australians actually derive from the legal opium production, but in any civilized country, issues of public health come before interests of commerce and law.

Submitted by Nevil Schoenmakers
Australia 14 February 2013

Mark Heinrich's Personal Issues Faced in Self Treatment of Medical Cannabis in Australia

I have worked incredibly hard these last years, trying to find my dignity and self respect again. To earn the respect back from my children and family. You see, I had lost all of that in the years of my active PTSD, and very nearly lost my freedom. I can not imagine what it would be like to slip back into that world, so that I can be a good citizen and obey the law. To once again become a legally prescribed addict stumbling around in a daze of prescribed pharmaceuticals.
In many aspects, I am being a good citizen by breaking this law, so that I can self medicate with my cannabis tinctures.
As I sit here wondering what tomorrow brings for me, I ask you to imagine yourself in my situation, then tell me it is fair and just that I cannot have my cannabis medicine? I re-live that memory every damn night when I do find sleep. Is it fair or just that my cannabis medicine should be taken from me? Would you do as I do and break a law to take an unconventional medicine? Of course you would! In a flash you would!
After a Federal Police raid on my home where I had people with guns walking through my house, I felt degraded and humiliated. I felt my human rights had been

violated. So I wrote to the Human Rights Commissioner and asked for help. I was basically told that due to laws as they are, the fact that I am being deprived of a life saving treatment is NOT an issue of human rights.

This is what I was sent. And what a lot of bullshit it is!

Dear Mark,
Thank you for your email to the Australian Human Rights Commission addressed to the Human Rights Commissioner. This email has been directed to the Complaint Handling Section, as the complaint handling powers are held by the President and not the Human Rights Commissioner. I apologise for not responding sooner.
In your email you say that the AFP raided your premises and confiscated cannabis products, which you say you need for your PTSD. You say that these actions are a breach of your human rights as contained in the Universal Declaration of Human Rights and the UN Charter.
Under the *Human Rights and Equal Opportunity Commission Act 1986* (HREOCA), this Commission can investigate complaints of human rights breaches by the Federal Government or one of its agencies. Under the legislation the definition of human rights is very specific and only includes those rights contained in the international instruments attached to the HREOCA. The Universal Declaration of Human Rights and UN Charter are not attached to the HREOCA.
I understand that this is a distressing situation for you, however it does not appear the issues you raise fall within this Commission's human rights provisions.
Therefore it does not appear Commission is the most appropriate body to assist.
It is unclear whether there is a pending court matter in regards to this issue. You may wish to seek some legal advice to see if there is any legal avenue available for you. You may wish to contact ACT Legal Aid on 1300 654 314.
If you have any further questions about this email, or this Commission's laws, feel free to contact me on 1300 656 419 or by return email.
Kind Regards,

Ben Crompton
Complaint Information Officer
Complaint Handling Section **Australian Human Rights Commission** (new name for the Human Rights and Equal Opportunity Commission)

Cannabis and Cancer

Through my work as a medical cannabis activist, and through my work as a researcher with Cannabis Science Australia, I am able to be closely involved with cannabis and patients looking to self treat with cannabis extracts. I will finish my submission with this article from Dr Manuel Guzman Professor of Biochemistry - University of Madrid

Cancer: Do cannabinoids cure cancer?

by Dr Manuel Guzmán January 2013

Cannabinoids, the active components of cannabis and their derivatives, exert palliative effects in cancer patients by preventing nausea, vomiting and pain and by stimulating appetite. In addition, these compounds inhibit the growth of tumour cells in laboratory animals -mice and rats. However, at the moment there is not solid evidence to prove that cannabinoids –whether natural or synthetic- can effectively treat cancer in patients, although research is ongoing around the world.

Comprehensive FAQ sections -including scientific references- on cannabinoids and cancer can be found at the Cancer Research UK website and the National Cancer Institute of the US website. Here that information is summarized and discussed.

What is cancer?

Cancer is a broad term used for diseases in which abnormal cells divide without control and are usually able to invade other tissues, causing metastases and high rates of mortality and morbidity. Cancer is not just one disease but many diseases: more than 100 different cancers are well-typified from a histopatological point of view by the WHO and, most likely, there are hundreds if not thousands types of cancers according to molecular and genetic profiling.

Most cancers are named for the organ or type of cell in which they start. In addition, cancer types are usually grouped into the following broader categories:

- Carcinoma: cancer that begins in the skin or in tissues that line or cover internal organs.
- Sarcoma: cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- Leukaemia: cancer that starts in blood-forming tissues such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.
- Lymphoma and myeloma: cancers that begin in the cells of the immune system.
- Central nervous system cancers: cancers that begin in the tissues of the brain and spinal cord.

Conclusion: Cancer is a very serious and heterogeneous disease, so fighting it therapeutically remains an extremely difficult challenge. Cannabinoids might therefore exert beneficial effects in some cancers but not in others.

Do cannabinoids inhibit cancer growth? (Laboratory research)

Virtually all the research into cannabinoids and cancer cells has been conducted so far using cancer cells grown in the lab or in animal models. Many scientific studies have reported that various cannabinoids (both natural and synthetic) exert a wide range of growth-inhibiting effects on cancer cells, including:

- Triggering cell death, through a mechanism called apoptosis.
- Stopping cells from dividing.
- Preventing new blood vessels from growing into tumours –a process termed

angiogenesis.
- Reducing the chances of cancer cells to metastasize through the body, by stopping cells from moving or invading neighbouring tissue.
- Speeding up the cell's internal 'waste disposal machine' –a process known as autophagy – which can lead to cell death.

Conclusion: Cannabinoids are efficacious drugs to treat at least some types of cancers in laboratory animals –mice and rats.

Do cannabinoids inhibit cancer growth? (Anecdotal evidence in humans)

As mentioned above, basically all the research investigating whether cannabinoids can treat cancer has been done in the lab. It is therefore important to be very cautious when extrapolating these results up to real live patients, who are a lot more complex than a Petri dish or a mouse. Anecdotal reports on cannabis use have been historically helpful to provide hints on the biological processes controlled by the endocannabinoid system and on the potential therapeutic benefits of cannabinoids. In the precise case of cancer there is a notable presence of videos and reports on the internet arguing that cannabis can cure cancer. These anecdotal claims may be completely or partially true in some cases, but overall remain –at least to date- weak and obscure. For example:

- We do not know whether the (supposed) effect of cannabis was due to a placebo effect.
- We do not know whether the tumour has (supposedly) stopped growing by natural/endogenous reasons -some tumours regress spontaneously/owing to the body's anti-tumour defences.
- We do not know how many patients have taken cannabis and have not obtained any therapeutic benefit, that is, what is the (supposed) efficacy of the cannabis-based therapy.
- As most likely patients have gone through standard therapy prior to or concomitantly with cannabis use, we do not know whether the (supposed) effect of cannabis was in fact due -at least in part- to the standard therapy -perhaps enhanced by cannabis, but we have no proof.
- We do not know what are the parameters of tumour progression that have been monitored and for how long the patient has been monitored -many potentially beneficial effects of antineoplastic drugs (or of cannabis in this case) are just short-term actions, but what about long-term progression-free survival and overall survival?
- Cancer is a very heterogeneous disease, and so far none has put together a sufficient number of patients for a particular type of cancer to support that cannabinoids are efficacious drugs in that precise cancer.

Conclusion: Although it is possible –and of course desirable- that cannabis preparations have exerted some antineoplastic activity in some particular cancer patients, the current anecdotal evidence reported on this issue is pretty poor, and, unfortunately, remains far from supporting that cannabinoids are efficacious anticancer drugs for large patient populations.

Do cannabinoids inhibit cancer growth? (Clinical research)

Results have been published from only one Phase I clinical trial testing whether cannabinoids can treat cancer in patients. Nine people with advanced, recurrent glioblastoma multiforme –an aggressive brain tumour– that had previously failed standard therapy were given highly purified THC through a catheter directly into their brain. Under these conditions cannabinoid delivery was safe and could be achieved without significant unwanted effects. In addition, although no statistically-significant conclusions can be extracted from such a small cohort of patients and without a control group, the results obtained suggested that some patients responded -at least partially- to THC treatment in terms of decreased tumour growth rate, as evaluated by imaging and biomarker analyses. These findings were encouraging and substantially reinforced the interest on the potential use of cannabinoids in cancer therapies. However, they also highlighted the need for further research aimed at optimizing the use of cannabinoids in terms of patient selection, combination with other anticancer agents and use of other routes of administration.

Conclusion: There are still many unanswered questions around the potential for using cannabinoids as anticancer drugs, and it is necessary and desirable that exhaustive clinical studies are conducted to determine how cannabinoids can be used, other than for their palliative effects, to treat cancer patients.

About the author

Dr Manuel Guzman is professor at the Department of Biochemistry and Molecular Biology at Complutense University in Madrid, Spain. He coordinates the Cannabinoid Signaling Group.

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