Physician Guidance for Medical Cannabis use

Overview of Pharmacology, Cannabis Therapeutic Mechanisms and Clinical Evidence

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BIOCHEMISTRY OF THE ENDOCANNABINOID SYSTEM (ECS)

The ECS is considered to be a complete biochemical system that has evolved across species, in part to regulate the stress response:

- Biological compounds, endocannabinoids, that activate G protein-coupled receptors: Anandamide (AEA) and 2-Arachidonoylglyerol (2-AG)
- Specific enzymes that synthesize eCB
- Specific binding sites (protein receptors) CB_1 and CB_2
- Specific enzymes that breakdown eCBs.

Vincenzo Di Marzo, a well-known cannabinoid researcher from Italy, has described the ECS as a system implicated in processes such as pain, perception, mood, memory and reward:

To provide that we:

- Eat
- Sleep
- Relax
- Forget
- Protect

PHARMACOLOGY OF CANNABINOIDS

Endocannabinoids are lipid transmitters made on demand from arachidonic acid in the cell membranes. By understanding the ECS scientists have been able to describe many of the physiological and behavioral effects that occur in animals and humans by interaction with plant cannabinoids (pCB). The pCBs most commonly studied are delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD). Theses compounds, native to the plant, are acid pre-cursors, and THC and CBD are heat transformation products. THC-acid (THCA) does not have the psychoactive effects of THC, nor does CBDA or CBD.

PHARMACOKINETICS OF CANNABINOIDS

Plant cannabinoids are highly bioavailable (10-30 %) when inhaled, and have a high volume of distribution (VD 10L/kg). 60-90% percent of the compounds are bound to lipoproteins and 3% are unbound in the blood stream. Peak plasma concentrations occur at about 6-10 minutes post-inhalation (similar to IV administration). The effects from inhalation are first felt from 0-10 minutes after inhaling, and last about 2-3 hours. (Table 1)

Orally administered, cannabinoids are less bioavailable due to first pass metabolism. Bioavailability is considered to be "erratic" with the onset of effect anywhere from 1-4 hours. After oral ingestion, metabolites remain active in the blood longer than with inhalation, potentially extending the effects to 6-10 hours. In particular, the metabolism of THC to 11-OH THC is notable because the metabolite has been reported to have greater potency at the CB1 receptor than delta-9 THC. THC binds to CB_1 receptor with higher affinity than the native ligands anandamide (AEA) or 2-arachidonylglyerol (2AG). It is estimated that about 1% of pCBs are able to penetrate the blood-brain barrier (with IV administration). Acute toxicity is very low, with no direct reports of mortality in humans from inhaling or ingesting Cannabis. Cannabinoids are metabolized by P450 enzymes, CYP2C19 and CYP3A4.

Fat burning will release pCBs back into the bloodstream, for an experience that has been termed "reintoxication". Thus, they may be detectable in the blood or urine long after inhalation or ingestion.

Table 1: Administration routes and kinetics

Route of Administration	Time to Take Effect	Duration of Relief
Inhalation	Almost immediate (1-3 min)	1 to 2 hours
Ingestion	30 minutes to 2 ½ hours	5 to 8 hours
Tincture	Almost immediate to 1 hour	2-4 hours

PHARMACODYNAMICS OF CANNABIS

The pharmacodynamics of cannabinoids is variable depending on the pCB. For example, THC has a strong binding affinity to the CB_1 receptor, compared to CBD, which has a very low affinity. Based on the wide distribution of the CB_1 receptor across the brain and other tissues, some effects of THC are: dilation of blood vessels, a decrease in body temperature, anti-emetic effects, changes in perception (specifically time perception) and balance, effects on immune function, short term memory changes and effects on learning. While not a strong agonist at CB_1, CBD has been described to reduce anxiety scores in animal behavior models, act as an anti-psychotic and an anti-inflammatory, These actions occur through binding at several other non-cannabinoid receptors (5HT1a, TRPV1, GPR18) and also may modulate the eCS by inhibition of the hydrolsis AEA.

It is significant that THC and CBD appear to have somewhat opposing action on psycho-activity and behavioral effects. The mechanisms of these effects have been somewhat unclear, however when administered together in human subjects, CBD modulated the psychoactivity of THC as observed using functional MRI. CBD also has the effects of delaying the onset of psychoactivity from THC, as well as prolonging it. (Bhattacharyya et al. 2010)

CANNABINOID AGONISTS VERSUS ANTAGONISTS

Endocannabinoids, are agonists at cannabinoid receptors, with THC acting as a potent agonist cannabinoid receptors, binding with higher affinity than the endogenous compounds.

Cannabinoids are reported to be “hormetics” or compounds that have a bi-phasic effect; agonists at a low concentration but appear to act as an antagonist at high concentration.

TOLERANCE

Tolerance develops to most of the acute effects of THC, such as cardiovascular (orthostatic hypotension and elevated heart rate), psychological (the “high”), analgesic, immunosuppression and skin hypothermia, over a period of several days. These changes are thought to be due to the down-regulation of the receptor, however in animal models this has not been proven. Some tolerance may also be due to desensitization of the receptor and also to metabolic changes.

CANNABIS RESEARCH

Taken together, the growing knowledge of the endocannabinoid system combined with anecdotal reports of people using Cannabis for various disorders, would rationalize clinical investigation. However, due to the Schedule I designation in the US, the National Institute on Drug Abuse (NIDA) funds Cannabis-related studies however every proposal to NIDA has been required to be framed as a study of drug abuse in order to receive funding and approval. Therefore, most human studies published in the US have been biased toward the study of Cannabis as a drug of abuse. (NIDA also is the only supplier of Cannabis for any approved clinical trials). This bias has caused a dearth of therapeutic studies and a weak clinical “evidence” base. Basic scientists can, however, receive funding to study cannabis and cannabinoids at the cellular level and in animal models.

CLINICAL APPLICATIONS

Cachexia/ Wasting Syndromes: Decreased appetite and food intake as a consequence of diseases such as positive HIV status (AIDS) or metastatic cancer, result in a negative energy balance, leading to weight loss. Wasting and loss of appetite are also associated with chemotherapy in cancer treatment (Tramer et al. 2001), neuropsychiatric conditions, various forms of dementia, normal aging, and anorexia nervosa. Since 1975, more than 35 studies have reported that either synthetic or isolated THC and smoked Cannabis have effectiveness for stimulating appetite and weight gain in cancer patients, with these therapeutic effects more extensively documented in AIDS patients. (Kirkham et al. 2002; Martin and Wiley 2004; Tramer et al. 2001) (**Table 2**)

HIV: Individuals with HIV constitute the largest group of patients who use cannabis for medical reasons. Cannabinoids are immune-modulatory and may have anti-viral effects. Smoked Cannabis has been shown to reduce HIV-neuropathy related pain (Abrams DI et al. 2007) but have no significant effects on immune phenotype or function (T-cell subsets) in these patients. (Bredt BM et al. 2002) A meta-analysis could not make any correlation with Cannabis use and survival in HIV+ patients. (Lutge 2013) Cannabis use has not been associated with adherence to ART, while dependent use or heavy use may negatively impact adherence. (Bonn-Miller et al. 2014) THC has been shown to inhibit cell migration, specifically by ablating neurologic sequela by migration of immune cells so the brain, and regular cannabis use was

shown in human subjects to decrease immune cell migration. (Raborn et al. 2014; Sexton et al. 2013). The palliative effects of Cannabis use are likely beneficial for patients with positive HIV status, and there is no evidence to suggest that this impairs immune function, but may be beneficial for the immune system and in have a role in preventing spread of HIV to the central nervous system.

Table 2:

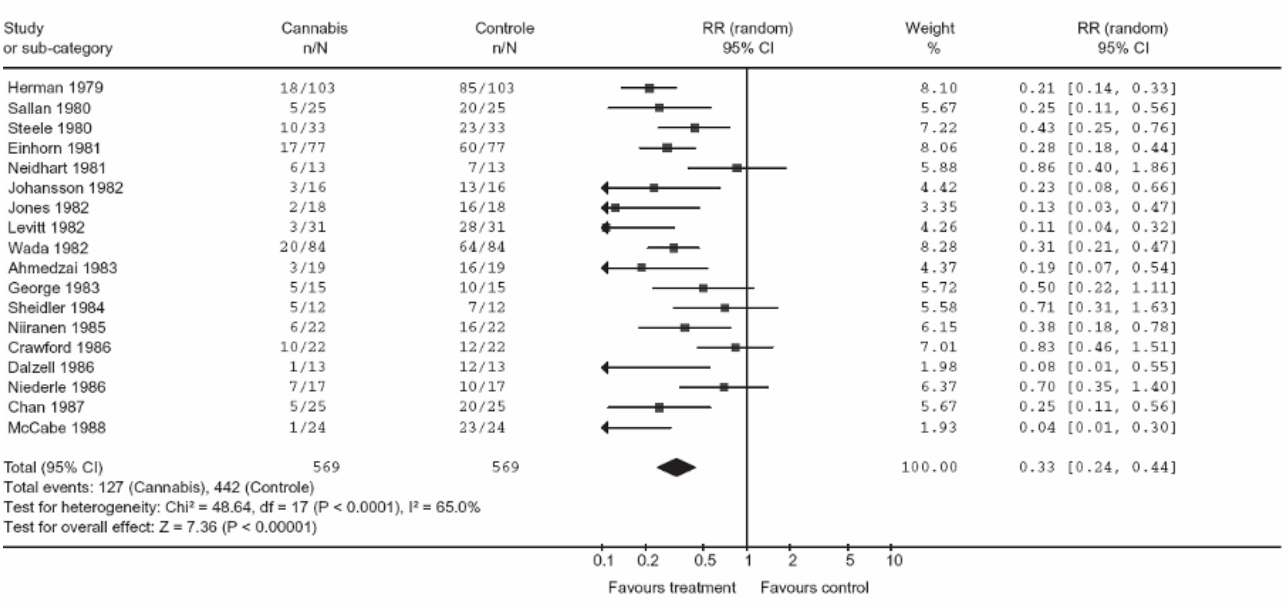

Figure 5. Preference for cannabis or control.

Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Rocha FCM, Oliveira LMQR, Da Silveira DX. 2008. *European Journal of Cancer Care*, Epub July 3.

<u>Inflammation and Motility: Inflammatory Bowel Disease (IBD: Crohn's):</u>

The proposed etiology of IBD is autoimmune inflammation that occurs in a chronic relapsing course, and affects over a million people in the United States. (Loftus 2004) (IBD includes ulcerative colitis (UC) and Crohn's disease (CD)). Cannabis has been has been known from antiquity to decrease emesis and diarrhea and to stimulate appetite. Current research shows the eCS to play an important role in controlling gastrointestinal motility and secretion. (Pertwee 2001; Pinto et al. 2002) Another role for cannabinoid signaling is in immunomodulation, as cannabinoid receptors are on immune cells where activation leads to increased activity of the eCS. (Klein TW et al. 1998; Walter and Stella 2004) These actions suggest modulation of the eCS as a therapeutic approach for IBD. Upregulation of CB_1 receptor has been measured in animal models, and cannabinoid receptor agonists have been shown to inhibit intestinal motility. Independent of the CB_1 receptor, anti-inflammatory action of CBD, as well as inhibition of AEA hydrolysis may be additional putative mechanisms. (Di Marzo 2011; Esposito 2012; Izzo AA and Sharkey KA 2010) One prospective placebo-controlled trial has been published, reporting that half of the patients discontinued daily use of conventional drugs due to the clinical

response. (Naftali et al. 2013) Patients used Cannabis cigarettes containing 115 mg THC each, twice daily and the cohort was followed for 10 weeks (n=21) and complete remission was achieved in 45% of subjects and there is a significant clinical steroid-free benefit to 10 of 11 patients with active disease. Another minor cannabinoid, cannabichromene (CBC) reduced GI hypermotility and slowed transit time in an experimental model of intestinal inflammation. (Izzo 2012) Patient-reported outcomes support the use of cannabis in controlling the debilitating symptoms of IBD. High CBD, oral ingestion may be the treatment of choice for these patients.

Parkinson Disease (PD):

The basal ganglia has abundant expression of `cannabinoid receptors and eCB serve as a 'feedback loop" for neurotransmitter release and the prospect of therapeutic potential by manipulation of this system is promising for several movement disorders. Overactivity' of glutamatergic release in PD contributes to progression of neuronal degeneration. The use of *Cannabis* in PD is predominantly for symptomatic control of tremor, improvement in bradykinesia, with additional putative benefit for muscle rigidity, psychosis, and levodopa-induced dyskinesia (LID). Evidence from case reports and surveys suggest benefit from smoked and oral consumption of crude *Cannabis* leaves. Forty-five percent of one patient population reported efficacy for general alleviation of PD-related symptoms. (Venderova 2004) There is a general paucity of formal human trial data on the use of *Cannabis* in either PD or LID. A recent review sought to determine safety and efficacy of cannabinoids in relieving the dyskinesias of PD. (Koppel 2013) One study examined CBD extract (1.25 or 2.5 mg) in 19 patients and showed no significant effects. It is unlikely that this dose would be therapeutically beneficial, especially in light of the fact of low oral bioavailability. Three reports of the use of CBD at doses higher than is generally achievable with typical smoking patterns demonstrated decreases in dystonia, pscyhosis, and total Unified Parkinson Disease Rating Scale (UPDRS) scores. (Zuardi 2006) Findings regarding use of orally consumed *Cannabis* leaves and CBD suggest that benefits are both dose- and duration-dependent. CBD was shown to control the symptom of REM sleep behavior disorder in patients with PD in a small case series.(Chagas 2014) Another study evaluated 22 patients after smoking Cannabis and found significantly improved UPDRS scores, as well as significant improvement in tremor, rigidity and bradykinesia and sleep and pain scores. (Lotan 2013) While we don't have a complete understanding of the role of the eCB in PD and LID, Cannabis has been shown to be well tolerated, and particular attention should be given to the presence of CBD in the plant when inhaled or in various preparations, and for LI-psychosis.

Multiple Sclerosis (MS) and Spasticity: The earliest recorded use of cannabis in the treatment of spasticity was from the 9th century BCE. Spasticity is a defining feature of MS, and can occur with other types of spinal cord injury or pathology. While there are more clinical studies of cannabis (extract) in MS than in any other diagnosis, the differences in dose, preparations, study designs and clinical endpoints have made it difficult to draw definitive conclusions, however, a number of studies support improvement in spasticity. (Wade DT et al. 2006; Zajicek JP et al. 2005) One study provides formal evidence of benefit from smoking Cannabis. (Corey-Bloom 2012) Cannabis extract has also been shown to be effective for

improving bladder control in patients with MS and to improve pain control. (Brady CM et al. 2004b; Iskedjian 2007; Kavia R et al. 2010) There is some additional preliminary evidence for the potential of cannabis to act as a disease-modifying therapy in MS, but due to the long-term and slow progressive nature of this disease, there need to be clear outcome measures defined to show the immune-modulatory benefit. This effect may be more associated with plants that are rich in CBD or at doses that would be more relevant for this effect (CBD:THC > 1). (Zajicek 2012) Evidence from trials using the Cannabis pharmaceutical Sativex™ demonstrate that there is potential for long-term benefit, and no tolerance, eliminating he need for continual upward titration of cannabinoids. Because MS is a disease associated with cognitive dysfunction, there has been little evidence showing a detrimental effect of cannabinoid therapy on cognitive function in patients with MS. Heavy use or long duration may modulate this effect, however. (Solowij 1995)

Epilepsy: Seizure control with Cannabis has been reported as early as the 1100 AD, and by Arabic writers from the 15th century. However, pro-convulsant effects of THC have also been reported, particularly on low (pre-drug) frequency seizure. There are case reports, case studies and surveys reporting improvement in seizure frequency and severity and that interaction with various drugs is limited. (Gross DW et al. 2004) An early study with 15 adults with partial seizure, administered CBD (≤ 300 mg/day) for four months, added on to existing drugs. The conclusion was that CBD may be of benefit to some patients. (Carlini EA and Cunha JM 1981) A recent survey of parents of pediatric patients with intractable epilepsy provided information on cannabidiol-rich extracts started at 0.5 mg/kg per day. (Porter 2013) Seizure frequency was reported by the parent to be reduced by 84%, along with benefits such as increased alertness, better mood and improved sleep. Twelve parents slowly weaned their child from other AEDs after beginning the therapy. The researchers controlled for their findings, using a similar questionnaire of parents who were not using Cannabis extract and concluded that there was high efficacy for the use of the CBD-rich extract. The available literature shows a general consensus that cannabis has an anti-convulsant action, although much of the evidence is subjective. Specific mechanisms of action for CBD are somewhat lacking, however the lack of toxicity or motor effects make it an attractive alternative for many AEDs and for patients who have seizure disorder unresponsive to them.

Post-Traumatic Stress Disorder (PTSD): The eCS is a natural therapeutic target for treating PTSD due to the role of this system in memory consolidation, retrieval and extinction. (Lutz 2007) The neuro-protective properties of cannabinoids are key to the therapeutic potential for PTSD. Animal studies have reinforced the effects of cannabinoids on improved sleep cycles, reduction in nightmares, extinction of adverse memories and abolishing anxiety, all symptoms reported by victims of PTSD. (Fraser 2009; Marsicano 2002; Passie 2012) New Mexico was the first state to include PTSD as a clinical diagnosis for the use of cannabis. A report out of that State showed a 75% reduction in Clinician-administered Post-traumatic Scale (CAPS: DSM-IV) when subjects were using cannabis compared to when they were not. (Greer 2014) Another study in a dispensary in California reported greater frequency of use in patients with PTSD who used it for sleep-promoting purposes with those who had higher scores. Sleep enhancement appears to be an important factor in consideration of frequency and timing of use.

(Bonn-Miller 2014) Animal research suggests an important role for CBD, acting at the 5HT1A receptor may be a putative mechanism to rationalize cannabis treatment in this population. (Campos 2012) More information is needed on dosing, routes of administration and timing after traumatic event. There have been no prospective trials with whole plant extracts. (Trezza 2013)

Glaucoma: A very early publication reported decrease in intraocular pressure by smoking cannabis and this result was extended to oral and topical administration. (Hepler RS and Frank IR 1971) The molecular mechanisms have been reviewed, and attributed to local action at the CB_1 receptor in the ciliary body. (Colasanti BK and SR. 1985 ; Järvinen T et al. 2002) Additional evidence for "supplementing" the eCS came from measuring low levels of eCB in eye tissues.(Chen J et al. 2005) There is good clinical evidence to support the use of ocular administration as well as smoked cannabis for treating intraocular pressure in patients with glaucoma. (Shapiro 1974) There has also been investigation into sublingual 5 mg THC, 20 mg CBD and 40 mg CBD with only the THC effective for reducing intraocular pressure. (Tomida et al. 2006)The presence of the eCS in the retina makes it an attractive target for a broad range of retinal disorders. (Yazulla 2008)

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